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Synchronization phenomena in nephron–nephron interaction

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Experimental data for tubular pressure oscillations in rat kidneys are analyzed in order to examine the different types of synchronization that can arise between neighboring functional units. For rats with normal blood pressure, the individual unit (the nephron) typically exhibits regular oscillations in its tubular pressure and flow variations. For such rats, both in-phase and antiphase synchronization can be demonstrated in the experimental data. For spontaneously hypertensive rats, where the pressure variations in the individual nephrons are highly irregular, signs of chaotic phase and frequency synchronization can be observed. Accounting for a hemodynamic as well as for a vascular coupling between nephrons that share a common interlobular artery, we develop a mathematical model of the pressure and flow regulation in a pair of adjacent nephrons. We show that this model, for appropriate values of the parameters, can reproduce the different types of experimentally observed synchronization. © *2001 American Institute of Physics.*
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The kidneys play an essential role in regulating the blood pressure and maintaining a proper environment for the cells of the body. This control depends to a large extent on mechanisms associated with the individual functional unit, the nephron. However, a variety of cooperative phenomena that arise from interactions among the nephrons may also be important. In-phase synchronization, for instance, where the nephrons simultaneously perform the same regulatory adjustments of the incoming blood flow is likely to produce fast and strong effects in the overall response to changes in the external conditions. Out-of-phase synchronization, on the other hand, will lead to a slower and less pronounced response of the system in the aggregate. The purpose of the present paper is to demonstrate how different forms of synchronization can be observed in the pressure and flow variations for neighboring nephrons. Particularly interesting is the observation of chaotic phase synchronization in rats with high blood pressure. Based on a description of the physiological mechanisms involved in the various regulations, we develop a mathematical model that can account for the experimentally observed synchronization phenomena.

I. INTRODUCTION

Physiological systems typically consist of a large number of functional units that interact via complex (heterogeneous) feedback structures to produce the required response on a higher organizational level. In many cases, the individual cell or functional unit already displays complicated nonlinear dynamic phenomena, and it is a challenge to physiology as well as to nonlinear science to explain how the coupling between the units influences the overall behavior.[1,2] In-phase synchronization, for instance, in which pulsatile or oscillatory units simultaneously perform the same adjustments in their functional behavior, is likely to produce synergetic effects in the overall response to external disturbances. Out-of-phase synchronization, on the other hand, will generate a slower and less pronounced response of the system in the aggregate, and waves that propagate across a group of interacting units can induce new oscillatory modes of behavior.

The insulin producing β cells of the pancreas represent a typical example. The β cells are known to show variations in their hormonal release that are related to complicated patterns of bursts and spikes in their membrane potentials.[3] Coupling between the cells takes place via a variety of different mechanisms, including the short-range diffusive exchange of ions and small molecules through gap junctions[4] and the response of the individual cell to variations in the intercellular Ca^{2+} concentration produced by the bursting activity of neighboring cells.[5] Hence, one can observe synchronization of the bursting activity between neighboring cells[6] as well as waves of cytoplasmic calcium propagating across groups of pancreatic cells.[7]

Transitions between different types of synchronization

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and between smaller and larger clusters of synchronized units may represent an important component in the overall regulation of a physiological system. Several cases are known where this type of transition is related to the development of a state of disease. It has long been recognized, for instance, that the onset of an epileptic seizure is associated with a synchronization of the firing activity for larger groups of cells in the brain.[8]

The purpose of the present paper is to demonstrate how different modes of synchronization can be observed in the pressure and flow regulation between neighboring functional units of the kidney and to develop a physiologically based model that can account for these phenomena. For rats with normal blood pressure, the observed synchronization effects include the presence of in-phase and antiphase synchronization between the regular oscillations of the proximal tubular pressures. For rats with spontaneously developed high blood pressure, our experimental results show evidence of chaotic phase and frequency synchronization.

II. PRESSURE AND FLOW CONTROL IN THE KIDNEY

The mammalian kidney contains a large number of similar functional units, the nephrons. For a human kidney the number of nephrons is of the order of 1 mil, and a rat kidney contains approximately 30 000. The nephrons are organized in a parallel structure such that each nephron processes a very small fraction of the total blood flow to the kidney, typically 200–300 nl/min for a rat nephron. To distribute the blood that enters through the renal artery, the kidney disposes of a strongly branched network of arteries and arterioles, and a similarly branched network collect the blood on the other side and leads it to the renal vein. Closest to the nephron we have the afferent arteriole that leads the blood to the capillary network in the glomerulus where filtration of water, salts, and small molecules from the blood into the tubular system of the nephron takes place. On the other side of the glomerulus, the efferent arteriole leads the blood into another capillary system that receives the water and salts reabsorbed by the tubules.

The sketch in Fig. 1 illustrates the arrangement of a group of glomeruli with their afferent arterioles branching off from an interlobular artery. Inspection of Fig. 1 reveals how nearly half the glomeruli sit in pairs with pieces of common arteriole (indicated by arrows).

In order to protect its function and secure a relatively constant supply of blood in the face of a highly variable arterial blood pressure, the individual nephron disposes of a number of control mechanisms. Most important is the so-called tubuloglomerular feedback (TGF) mechanism[9,10] that regulates the diameter of the afferent arteriole in dependence of the ionic composition of the fluid that leaves the loop of Henle via the distal tubule. If the NaCl concentration of this fluid becomes too high, specialized cells (macula densa cells) near the terminal part of the ascending limb of the loop of Henle elicit a feedback signal that causes the smooth muscle cells around the downstream end of the afferent arteriole to contract and, hence, reduce the incoming blood flow and the rate of filtration.

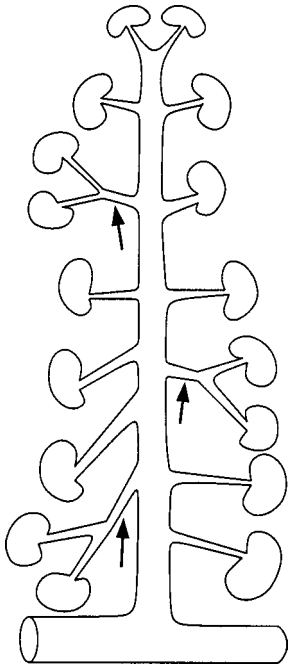

FIG. 1. Typical arrangement of a group of glomeruli with their afferent arterioles branching off from the same interlobular artery.

The TGF mechanism is a negative feedback regulation. However, in the mid-1980s, experiments by Leyssac and Baumbach[11] and by Holstein-Rathlou and Leyssac[12] demonstrated that the TGF regulation in rat nephrons tends to be unstable and to generate self-sustained oscillations in the tubular pressures and flows with a typical period of 30–40 s. While for normal rats the oscillations had the appearance of a regular self-sustained oscillation with a sharply peaked power spectrum, highly irregular oscillations, displaying a broadband spectral distribution with strong subharmonic components, were observed for spontaneously hypertensive rats. It has subsequently been found that irregular oscillations can be elicited for rats with normal blood pressure, provided that the arterial blood pressure is increased by reducing the blood flow to the other kidney (two-kidney, one-clip Goldblatt hypertensive rats). In a particular experiment[13] where the function of the nephron was temporarily disturbed, a period doubling of the pressure oscillations was observed. This gives strong evidence for the system operating close to a transition to chaos.

The steady state response of the TGF mechanism can be obtained from open-loop experiments[14] in which a paraffin block is inserted into the middle of the proximal tubule, and the rate of filtration is measured as a function of an externally forced flow of artificial tubular fluid into the loop of Henle. This response follows an S-shaped characteristic with a maximum at low Henle flows and a lower saturation level at externally forced flows beyond 20–25 nl/min. The steepness of the response is found to be significantly higher for spontaneously hypertensive rats than for normotensive rats.[15] Together with the delay in the TGF regulation, this steepness plays an essential role for the stability of the feedback system. The length of the regulatory delay can be estimated from the phase shift between the pressure oscillations in the

proximal tubule and the oscillations of the NaCl concentration in the distal tubule. A typical value is 10–15 s.[16] In addition there is a transmission time of 3–5 s for the signal from the macula densa cells to reach the smooth muscle cells in the arteriolar wall. In total this delay is sufficient for the nephrons in normotensive rats to operate close to or slightly beyond a Hopf bifurcation point.

Besides reacting to the TGF signal, the afferent arteriole also responds to changes in its transmural pressure. The significance of this element in the nephron pressure and flow regulation is clearly revealed in experiments where the spectral response to a noise input is determined.[16] Here, one observes a peak at frequencies considerably higher than the frequencies of the TGF regulation and corresponding to typical arteriolar dynamics. Based on *in vitro* experiments on the strain–stress relationships for muscle strips, Feldberg *et al.*[17] have proposed a mathematical model for the reaction of the arteriolar wall in the individual nephron.

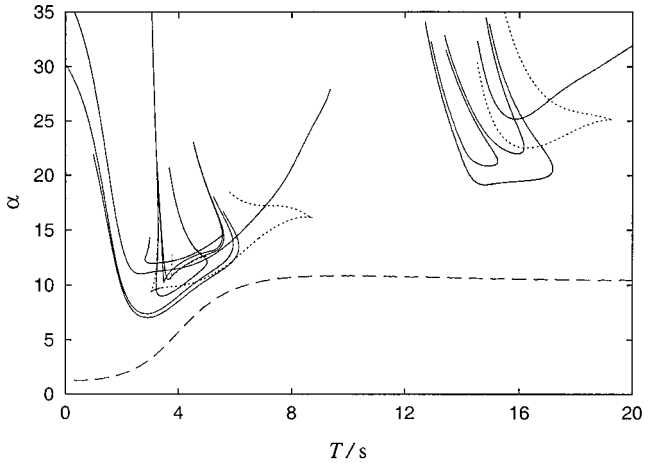

FIG. 2. Two-dimensional bifurcation diagram for the single-nephron model. T is the total delay in the tubuloglomerular feedback, and α is the slope of the feedback characteristics. The dashed curve is a Hopf bifurcation curve. Period-doubling and saddle-node bifurcation curves are shown as fully drawn or dotted curves. The physiologically realistic region is around $T=16$ s and $\alpha=11-18$.

III. NEPHRON–NEPHRON INTERACTION

As previously noted, the nephrons are typically arranged in couples or triplets with their afferent arterioles branching off from a common interlobular artery, and this proximity allows them to interact in various ways. Early experimental results by Holstein-Rathlou[18] showed how neighboring nephrons tend to adjust their TGF-mediated pressure oscillations so as to attain a state of in-phase synchronization. Holstein-Rathlou has also demonstrated how microperfusion with artificial tubular fluid of one nephron affects the amplitude of the pressure variations in a neighboring nephron.

The mechanisms underlying this cross-talk among the nephrons are not known in detail. However, in view of the structure of the system and the observed characteristics of the synchronization phenomena, two different types of interaction seem to be involved.

(i) A coupling caused by interaction between the TGF regulations of neighboring nephrons. The presence of such an interaction is well established experimentally, but the underlying cellular mechanisms remain unresolved. Presumably the coupling is due to a so-called vascularly propagated response where electrochemical signals, initiated by the TGF, propagate across the smooth muscle cells in the arteriolar wall from the region close to the macula densa and upstream along the afferent arteriole to the branching point with the arteriole from the neighboring nephron. Because of the relatively high speed at which such signals propagate as compared with the length of the vessels and the period of the TGF-mediated oscillations, this type of coupling tends to produce in-phase synchronization. If the afferent arteriole of one nephron is stimulated by the TGF mechanism to contract, the vascularly propagated signals almost immediately reach the neighboring nephron and cause it to contract as well. We denote this type of coupling as vascular coupling.

(ii) A much simpler type of interaction that we shall refer to as hemodynamic coupling. This coupling arises from the fact that if one nephron is stimulated by its TGF mechanism to contract its afferent arteriole, then the hydrostatic pressure rises over the neighboring nephron, and the blood flow to this nephron increases. Half a period later when the increased blood flow activates the TGF mechanism in the neighboring nephron and causes it to contract its afferent arteriole, the blood flow to this nephron is again reduced, and the blood flow to the first nephron increases. This type of coupling tends to produce out-of-phase or antiphase synchronization between the pressure oscillations of the two nephrons. In reality, we expect both mechanisms to be present simultaneously. Depending on the precise structure of the arteriolar network this may cause one mechanism to be the stronger in certain parts of the kidney and the other mechanism to dominate in other parts.

Over the years a variety of different models have been proposed to describe the dynamics of the pressure and flow regulation for the individual nephron.[19,13] Most recently, Barfred *et al.*[20] have developed a model that provides a relatively detailed account of the nonlinear phenomena arising through the response of the afferent arteriole to the feedback signal from the macula densa cells. The present work is based on a coupling of two such single-nephron models. Models of systems of interacting nephrons have previously been published by Jensen *et al.*[13] and by Bohr *et al.*[21] However, these studies were performed before the actual physiological mechanisms responsible for the coupling were known.

Figure 2 shows an extended version of the two-dimensional bifurcation diagram obtained by Barfred *et al.*[20] In this diagram the parameter T along the horizontal axis measures the total delay in the tubuloglomerular feedback. As previously noted, this delay is typically of the order of $T\cong 16$ s. The parameter α along the vertical axis represents the slope of the feedback characteristics (compare with the equations of motion in Ref. 20). The lowest (dashed) curve in the figure is a Hopf-bifurcation curve. Below this curve, the nephron displays a stable equilibrium state. For values of the loop gain α above the Hopf-bifurcation curve, however, the pressure and flow regulation in the individual nephron is

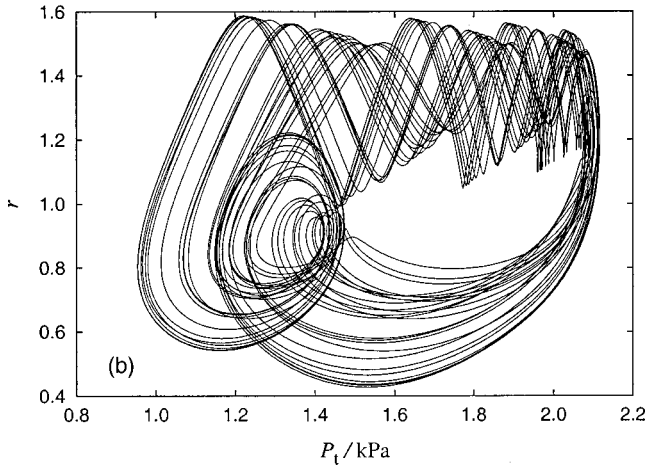

FIG. 3. Phase plot of the chaotic attractor that exists in the single-nephron model for $T=16$ s and $\alpha=32$. r is the normalized arteriolar radius and P_t the proximal tubular pressure. The arteriolar system performs 4–5 oscillations for each period of the TGF mediated oscillations.

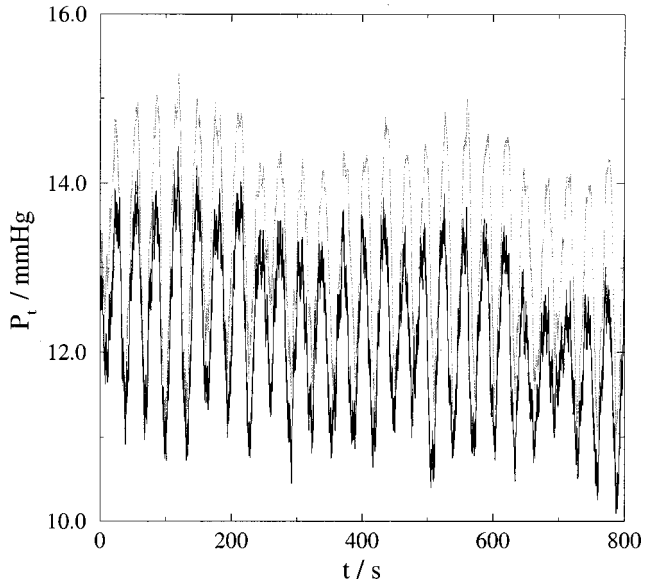

FIG. 4. Tubular pressure variations for a pair of coupled nephrons in a normotensive rat.

unstable, and self-sustained oscillations (or more complicated dynamics) can be observed. Typical values for the loop gain are $\alpha\cong 12$ for normotensive rats and $\alpha\cong 17$ for hypertensive rats.[15]

Compared with the original bifurcation diagram (Fig. 6 of Ref. 20), Fig. 2 includes a new region of overlapping period-doubling (fully drawn) and saddle-node (dotted) bifurcation curves for feedback delays in the physiologically relevant regime around $T=16$ s. These structures, which may be compared with the cross-road and spring-area structures known for one- and two-dimensional maps,[22,23] arise through resonances between the tubuloglomerular feedback and the oscillations characterizing the arteriolar response. The bifurcation structure to the left in the diagram (around $T=4$ s) is associated with the overlapping 1:1, 1:2, and 1:3 resonances of the two oscillatory modes, and the structure near $T=16$ s arises from the overlapping 1:4, 1:5, and 1:6 resonances.[24]

To illustrate the interaction between the two different oscillatory modes, Fig. 3 shows a phase plot of the chaotic attractor that can be observed in the single-nephron model for $\alpha=32$ and $T=16$ s. In Fig. 3 we have plotted simultaneous values of the (normalized) arteriolar radius r and of the proximal tubular pressure P_t. With the assumed parameters the arteriolar radius performs four to five oscillations for each period of the TGF mediated oscillations. As previously noted, both of these oscillatory components can be observed in experiments where the spectral response of the tubular pressure to a noise input is measured.[16] The chaotic attractor in Fig. 3 is also similar to the attractors that one can obtain through reconstruction (in terms of delay variables) of experimental results for the proximal tubular pressure in hypertensive rats.[13] The chaotic nature of the pressure variations is supported by a series of studies[19,13,20,25] applying a variety of different techniques, most recently by a work[26] in which the experimental time series have been fitted to a nonlinear autoregressive model, and the presence of deterministic dynamics with a positive Lyapunov exponent has been demonstrated.

IV. EXPERIMENTAL RESULTS

Experiments were performed with normotensive as well as with spontaneously hypertensive rats.[27] During the experiments the rats were anesthetized, placed on a heated operating table to maintain the body temperature, and connected to a small animal respirator to ensure a proper oxygenation of the blood. The frequency of the respirator was close to 1 Hz. This component is clearly visible in the frequency spectra of the observed tubular pressure variations. Also observable is the frequency of the freely beating heart, which typically gives a contribution in the 4–6 Hz regime. The frequencies involved in the nephron pressure and flow regulation are significantly lower and, presumably, not influenced much by the respiratory and cardiac forcing signals.[13]

When exposing the surface of a kidney, small glass pipettes, allowing simultaneous pressure measurements, could be inserted into the proximal tubuli of a pair of adjacent, superficial nephrons. After the experiment, a vascular casting technique was applied to determine if the considered nephron pair shared a common piece of afferent arteriole. Only nephrons for which such a shared arteriolar segment was found showed clear evidence of synchronization, supporting the hypothesis that the nephron–nephron interaction is mediated by the network of incoming blood vessels.[28,29]

Figure 4 shows an example of the tubular pressure variations that one can observe for adjacent nephrons for a normotensive rat. For one of the nephrons, the pressure variations are drawn in black, and for the other nephron in gray. Both curves show fairly regular variations in the tubular pressures with a period of approximately 31 s. The amplitude is about 1.5 mm Hg and the mean pressure is close to 13 mm Hg. Inspection of Fig. 4 clearly reveals that the oscillations are synchronized and remain nearly in phase for the entire observation period (corresponding to 25 periods of oscillation).

Figure 5 shows an example of the opposite type of syn-

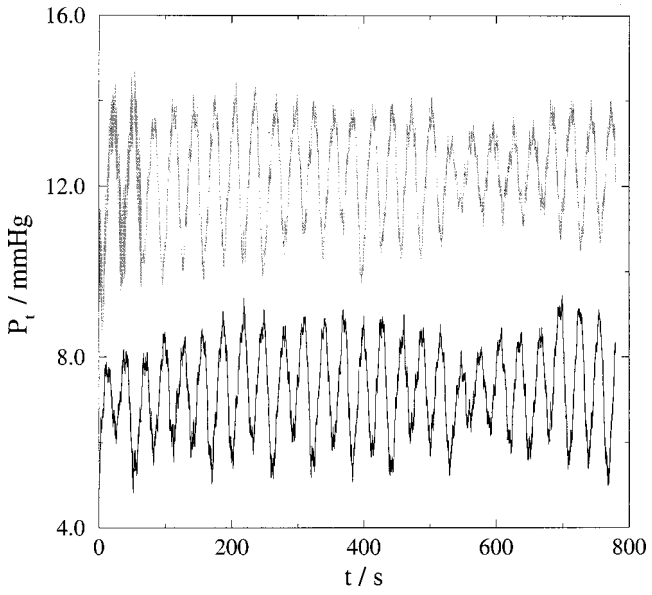

FIG. 5. Antiphase synchronization in the pressure variations for two neighboring nephrons in a normotensive rat. This type of synchronization is considered to be associated with a strong hemodynamic component in the coupling.

chronization where the nephrons operate nearly 180° out of phase. These results are also from a normotensive rat. As previously mentioned, we consider antiphase synchronization to be the signature of a strong hemodynamic component in the coupling, i.e., contraction of the afferent arteriole for one nephron causes the blood flow to the adjacent nephron to increase. In line with this interpretation, inspection of the vascular tree has shown that the nephrons in this case, while sharing an interlobular artery, are too far apart for the vascularly propagated coupling to be active.

Figures 6(a) and 6(b) show examples of the tubular pressure variations in pairs of neighboring nephrons for hypertensive rats. These oscillations are significantly more irregular than the oscillations displayed in Figs. 4 and 5 and, as previously discussed, it is likely that they can be ascribed to a chaotic dynamics.[19,13,20,25] In spite of this irregularity, however, one can visually observe a certain degree of synchronization between the interacting nephrons. Figure 7 reproduces the results of a frequency analysis of the two pressure signals in Fig. 6(b). One can immediately identify the respiratory forcing signal at 1 Hz. The TGF-mediated oscillations produce the peak around 0.03 Hz, and the arteriolar oscillations show up as a relatively broad peak around 0.2 Hz. One can see how the spectral lines coincide for both the arteriolar oscillations and the TGF mediated oscillations. This implies that these oscillations are synchronized in frequency between the two interacting nephrons.

In order to investigate the problem of phase synchronization for the irregular pressure variations in hypertensive rats we have applied the method introduced by Rosenblum *et al.*[30,31] With this approach one can follow the temporal variation of the difference $\Delta\Phi(t)=\Phi_2(t)-\Phi_1(t)$ between the instantaneous phases $\Phi_1(t)$ and $\Phi_2(t)$ for a pair of coupled chaotic oscillators. The instantaneous phase $\Phi(t)$

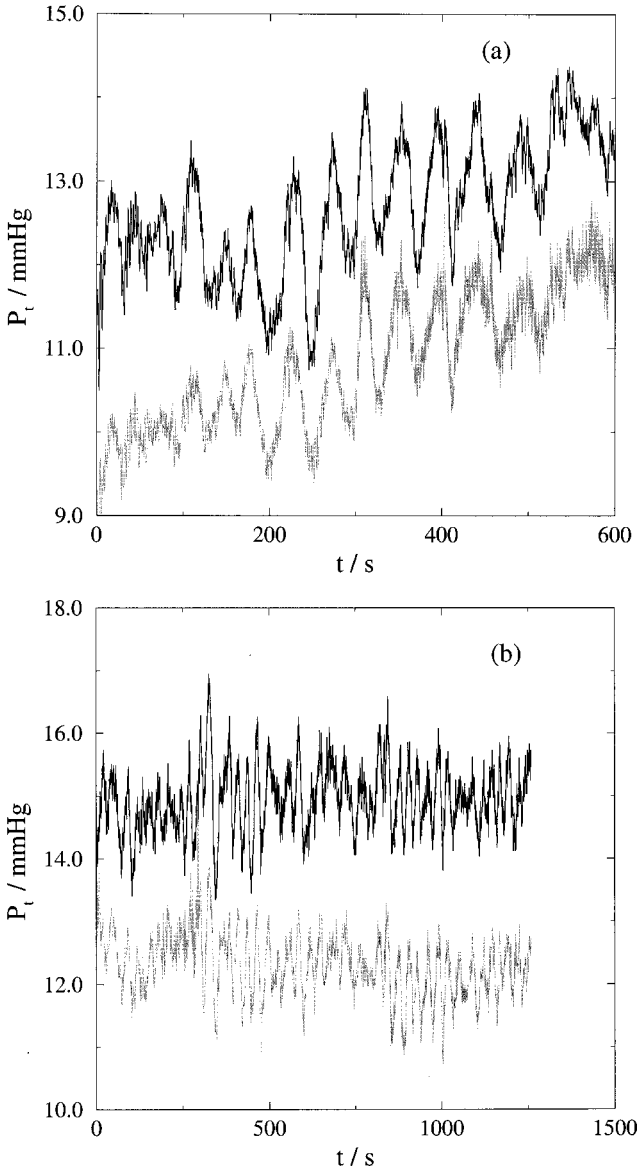

FIG. 6. Two examples [(a) and (b)] of the tubular pressure variations that one can observe in adjacent nephrons for hypertensive rats.

and amplitude $A(t)$ for a signal $s(t)$ with irregular (chaotic) dynamics may be defined from

$$A(t)e^{j\Phi(t)}\equiv s(t)+j\tilde{s}(t), \tag{4.1}$$

where

$$\tilde{s}(t)=\frac{1}{\pi}PV\int_{-\infty}^{\infty}\frac{s(\tau)}{t-\tau}d\tau \tag{4.2}$$

denotes the Hilbert transform of $s(t)$, j being the imaginary unit. The notation PV implies that the integral should be evaluated in the sense of Cauchy principal value.

$m:n$ phase synchronization between two oscillators is said to occur if

$$|n\Phi_2(t)-m\Phi_1(t)-C|<\mu, \tag{4.3}$$

where μ is a small parameter ($\mu<2\pi$) that controls the allowed play in the phase locking. In particular, 1:1 phase synchronization is realized if the phase difference $\Phi_2(t)$

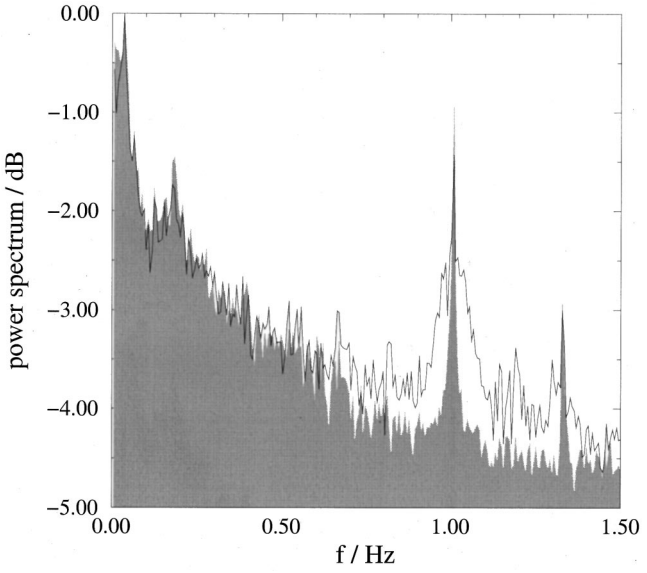

FIG. 7. Spectral distribution of the irregular pressure variations in Fig. 6(b). The peak at 1 Hz is the respiratory forcing signal.

$-\Phi_1(t)$ remains bound to a small interval μ around a mean value C. For systems subjected to external disturbances or noise one can only expect the condition for phase synchronization to be satisfied over finite periods of time, interrupted by characteristic jumps in $\Delta\Phi$. Under these circumstances one can speak about a certain degree of phase synchronization if the periods of phase locking become significant compared to the characteristic periods of the interacting oscillators.[32] Alternatively, one can use the concept of frequency synchronization if the weaker condition

$$\Delta\Omega = \langle n\dot{\Phi}_2(t) - m\dot{\Phi}_1(t)\rangle = 0$$

is satisfied. Here, $\langle\,\rangle$ denotes time average, and $\Delta\Omega$ is the difference in (mean) angular frequencies. As noted previously, 1:1 frequency synchronization is already distinguishable from the spectral distribution of the experimental data.

Figure 8(a) shows the variation of the normalized phase difference $\Delta\Phi/2\pi$ for the irregular pressure oscillations in Fig. 6(a). One can clearly see the locking intervals with intermediate phase slips. In particular, there is relatively long interval from $t\cong 160$ s to $t\cong 460$ s (corresponding approximately to six oscillations of the individual nephrons) where the phase difference remains practically constant. Figure 8(b) reproduces similar results for the irregular pressure variations in Fig. 6(b). Here, we note in particular the interval from $t\cong 400$ s to $t\cong 600$ s (corresponding to eight oscillations of the individual nephrons) where the phase difference remains nearly constant. We also note that the phase slips typically assume a value of 2π (or an integer number of 2π jumps).

We have measured and analyzed the tubular pressure variations for about ten pairs of chaotically oscillating nephrons. In most cases we have found indication of frequency synchronization and in some cases of phase synchronization. However, the above two examples [Figs. 8(a) and 8(b)] remain among the best. When judging this result, one has to consider that each nephron is surrounded by, and with varying strengths coupled to, several other nephrons. It should also be noted that, because of the interacting TGF-mediated and arteriolar oscillations, the chaotic dynamics in the nephrons is fairly complex and, hence, difficult to synchronize.[24]

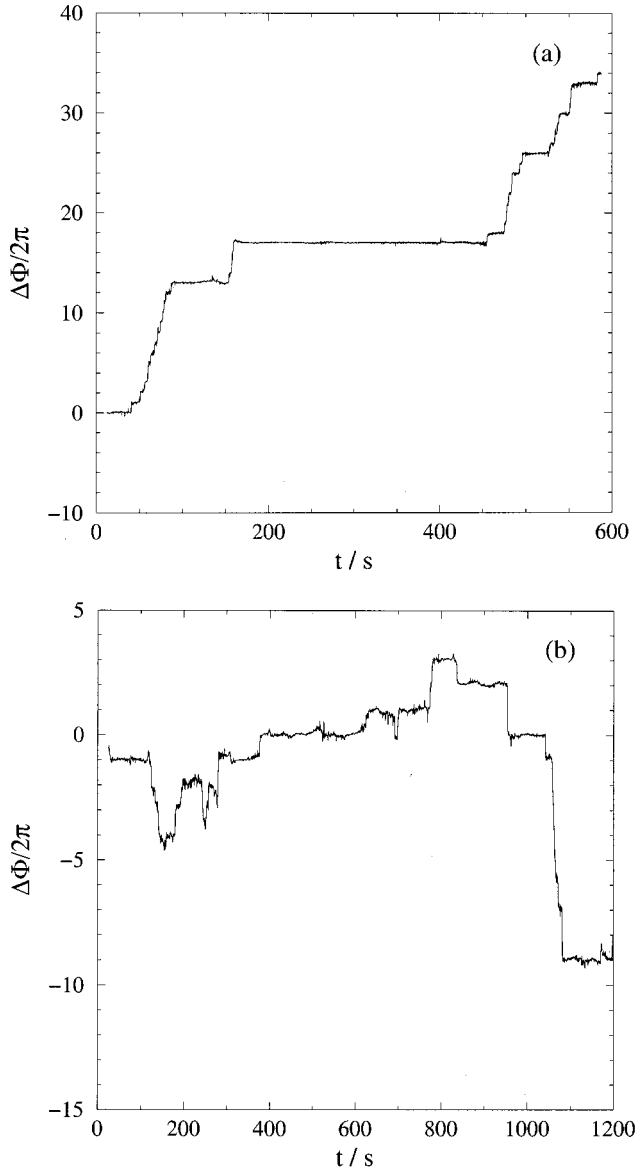

FIG. 8. Variation of the normalized phase difference $\Delta\Phi/2\pi$ for the irregular pressure variations in Figs. 6(a) and 6(b).

For comparison with the results obtained for the chaotically oscillating nephrons, Figs. 9(a) and 9(b) display the calculated variations in the normalized phase difference for the regularly oscillating nephron pairs in Figs. 4 and 5, respectively. For the interacting nephrons in Fig. 4, the phase difference is found to move in a narrow interval around $\Delta\Phi/2\pi = 0$, although with a tendency for the phase locking to destabilize toward the end of the trace. For the nephrons in Fig. 5, the phase difference moves around $\Delta\Phi = \pi$, indicating the occurrence of antiphase synchronization.

V. MODELING NEPHRON–NEPHRON INTERACTION

As previously noticed, the nephrons are often arranged in pairs or triplets that share a common interlobular artery.

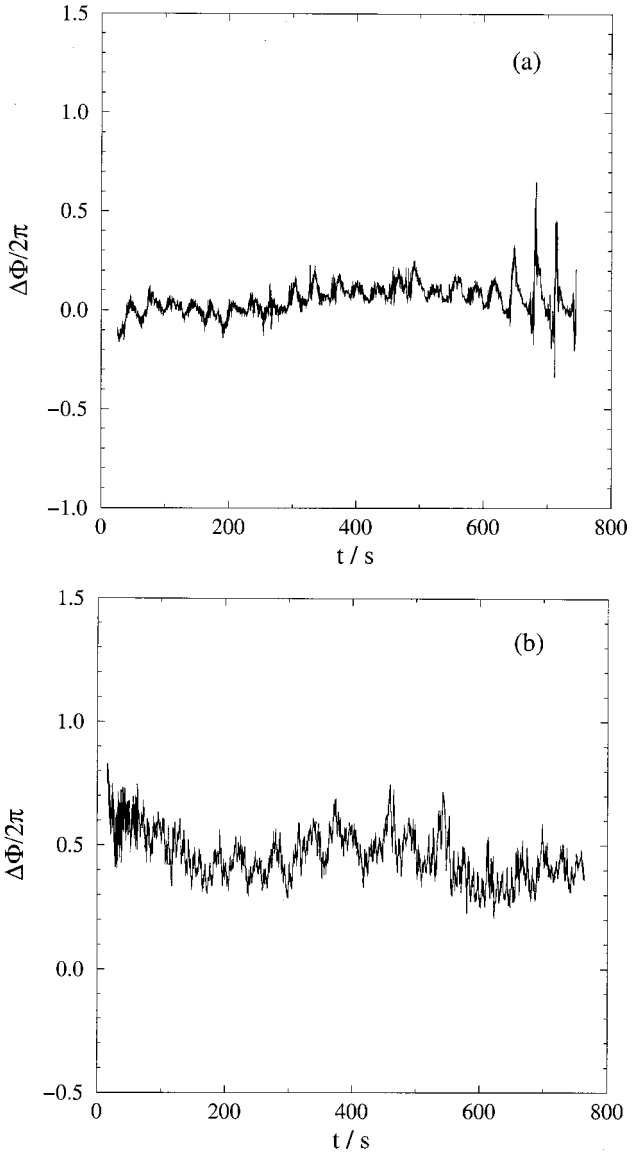

FIG. 9. Normalized phase difference for the regular pressure variations in Figs. 4 (a) and 5(b). Here one can clearly observe both in-phase ($\Delta\Phi \cong 0$) and antiphase ($\Delta\Phi \cong \pi$) synchronization.

Besides possible other mechanisms of interaction, this anatomical feature allows neighboring nephrons to influence each others blood supply either through electrical signals that activate the vascular smooth muscle cells of the neighboring nephron or through a direct hemodynamic coupling. The two mechanisms depend very differently on the precise structure of the arteriolar network. Hence, variations of this structure may determine which of the mechanisms dominates. This is of considerable biological interest, because the signals produced by the two mechanisms tend to be opposite in phase, and their influence on the overall behavior of the nephronic system may be very different.

Let us start by considering the vascularly propagated coupling. The muscular activation ψ (compare the single-nephron model in Ref. 20) arises in the juxtaglomerular apparatus and travels backwards along the afferent arteriole in a damped fashion. When it reaches the branching point with the arteriole from the neighboring nephron, it may propagate in the forward direction along this arteriole and start to contribute to its vascular response. In our model this type of cross-talk is represented by adding a contribution of the activation of one nephron to the activation of the other, i.e.,

$$\psi_{1\,\mathrm{tot}} = \psi_1 + \gamma\psi_2,$$

$$\psi_{2\,\mathrm{tot}} = \psi_2 + \gamma\psi_1,$$

where γ is the vascular coupling parameter, and ψ_1 and ψ_2 are the uncoupled activation levels of the two nephrons as determined by their respective TGF signals.

As previously mentioned, the vascular signals propagate very fast as compared with the length of the vessels relative to the period of the TGF oscillations. Hence, as a first approach, the vascular coupling can be considered as instantaneous. Experimentally one observes[29] that the magnitude of the activation decreases exponentially as the signal travels along a vessel. Only a fraction of the activation from one nephron can therefore contribute to the activation of the neighboring nephron, and $\gamma = e^{-l/l_0} < 1$. Here, l is the propagation length for the coupling signal, and $l_0 \cong 200\,\mu$m is the characteristic length scale of the exponential decay. As a base case value, we shall use $\gamma = 0.2$.

To implement the hemodynamic coupling, a piece of common interlobular artery is included in the system, and the total length of the incoming blood vessel is hereafter divided into a fraction $\varepsilon < \beta$ that is common to the two interacting nephrons, a fraction $1-\beta$ that is affected by the TGF signal, and a remaining fraction $\beta - \varepsilon$ for which the flow resistance is considered to remain constant. As compared with the equilibrium resistance of the separate arterioles, the piece of shared artery, carrying twice the blood flow, is assumed to have half the flow resistance per unit length.

Defining P_ε as the pressure at the branching point of the two arterioles, the equation of continuity for the blood flow reads

$$\frac{P_a - P_\varepsilon}{\varepsilon R_{a0}/2} = \frac{P_\varepsilon - P_{g,1}}{R_{a,1}} + \frac{P_\varepsilon - P_{g,2}}{R_{a,2}} \tag{5.1}$$

with the flow resistances

$$R_{a,1} = (\beta - \varepsilon)R_{a0} + (1-\beta)R_{a0}r_1^{-4} \tag{5.2}$$

and

$$R_{a,2} = (\beta - \varepsilon)R_{a0} + (1-\beta)R_{a0}r_2^{-4}. \tag{5.3}$$

Here, R_{a0} denotes the total flow resistance for each of the two nephrons in equilibrium. r_1 and r_2 are the normalized radii of the active part of the afferent arterioles for nephron 1 and nephron 2, respectively, and $P_{g,1}$ and $P_{g,2}$ are the corresponding glomerular pressures. As a base value of the hemodynamic coupling parameter we shall use $\varepsilon = 0.2$.

Because of the implicit manner in which the glomerular pressure is related to the efferent osmotic pressure and the filtration rate, direct solution of the set of coupled algebraic equations for the two-nephron system becomes rather inefficient. Hence, for each nephron we have introduced the glomerular pressure P_g as a new state variable determined by

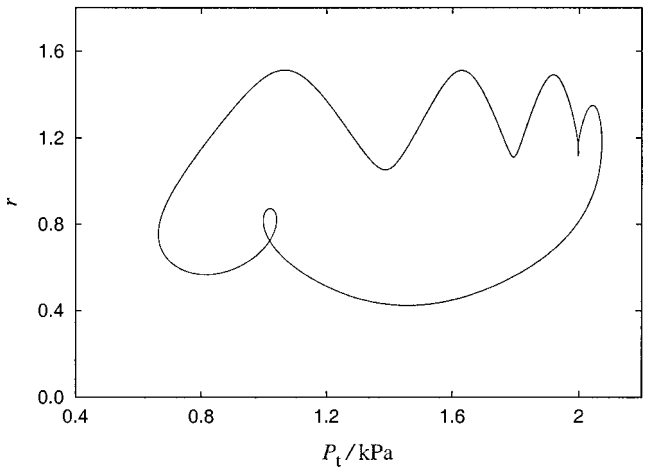

FIG. 10. Phase plot for the steady-state behavior of one of the nephrons in the coupled nephron model. $\gamma=\varepsilon=0.2$. The two nephrons are assumed to have identical parameters, and with $T=16$ s and $\alpha=12$ the uncoupled nephrons perform identical periodic motions (with arbitrary phase relations).

$$\frac{dP_{g,i}}{dt}=\frac{1}{C_{\mathrm{glo}}}\left(\frac{P_{\varepsilon}-P_{g,i}}{R_{a,i}}-\frac{P_{g,i}-P_{v}}{R_{e}}-F_{\mathrm{filt},i}\right) \tag{5.4}$$

with $i=1,2$. This implies that we consider the glomerulus as an elastic structure with a compliance C_{glo} and with a pressure variation determined by the imbalance between the incoming blood flow $(P_{\varepsilon}-P_{g,i})/R_{a,i}$, the outgoing blood flow $(P_{g,i}-P_{v})/R_{e}$, and the glomerular filtration rate $F_{\mathrm{filt},i}$.

Compared with the compliance of the proximal tubule, C_{glo} is considered to be quite small, so that the model becomes numerically stiff. In the limit $C_{\mathrm{glo}}\to 0$, the set of differential equations reduces to the formulation with algebraic equations used by Barfred *et al.*[20] Finite values of C_{glo} will change the dynamics of the system, and therefore also the details of the bifurcation structure. In practice, however, the model will not be affected significantly as long as the time constant $C_{\mathrm{glo}}R_{\mathrm{eff}}$ remains small compared with the periods of interest. Here, R_{eff} denotes the effective flow resistance faced by C_{glo}.

Figure 10 shows a phase plot for the steady-state behavior of one of the nephrons in the coupled-nephron model. Here, we have displayed the normalized radius of the active part of the afferent arteriole versus the proximal tubular pressure for $\gamma=\varepsilon=0.2$. The two nephrons are assumed to have identical parameters, and with $T=16$ s and $\alpha=12$ the uncoupled nephrons perform identical periodic motions with an arbitrary relation between their phases. Figure 10 shows the motion generated by the relatively slow TGF-mediated oscillations in combination with the faster arteriolar oscillations. With the considered parameters these two oscillations are entrained in a 1:5 synchronization. Introducing a coupling forces the nephrons to synchronize their phases. Depending on the initial conditions and on the relative strengths of the two coupling mechanisms this synchronization may be either in phase or in antiphase.

A typical example of antiphase synchronization is demonstrated by the temporal variations of the tubular pressures of the two periodically oscillating nephrons in Fig. 11. Here,

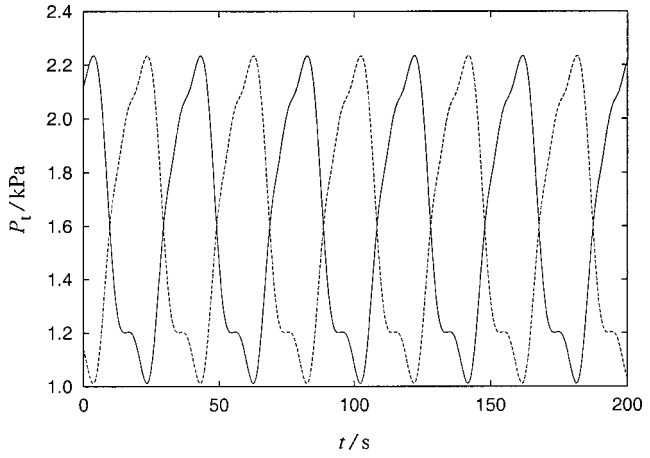

FIG. 11. Typical example of antiphase synchronization in the tubular pressures of two periodically oscillating nephrons. $T=16$ s, $\alpha=12$, $\varepsilon=0.3$, and $\gamma=0.05$.

$T=16$ s, $\alpha=12$, $\varepsilon=0.3$, and $\gamma=0.05$. With these parameters, the hemodynamic coupling dominates, and the nephrons operate nearly 180° out of phase.

Let us hereafter consider the situation for larger values of α where the individual nephron exhibits chaotic dynamics. Figure 12(a) shows a phase plot for one of the nephrons in

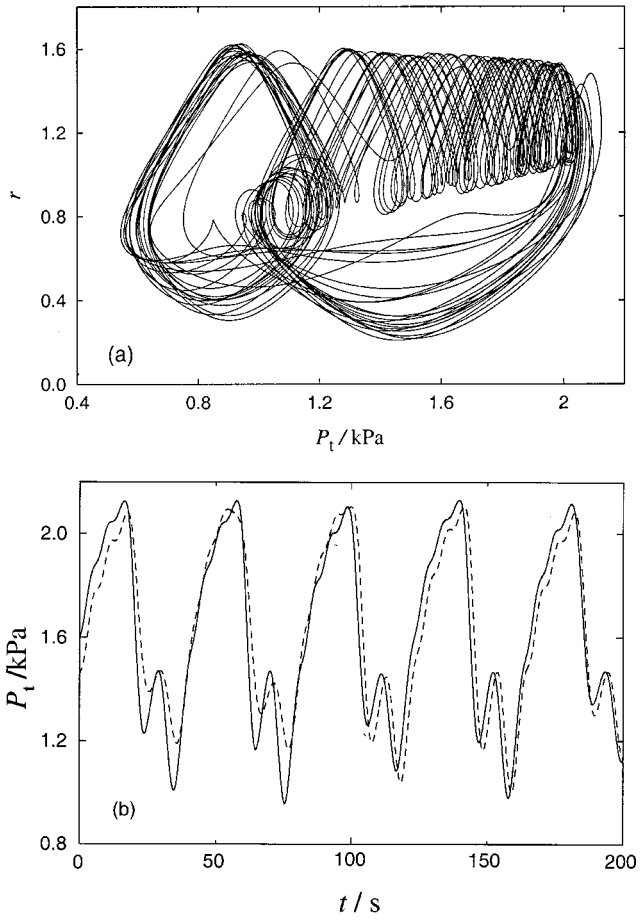

FIG. 12. Phase plot for one of the nephrons (a), and temporal variation of the tubular pressures for a pair of coupled chaotically oscillating nephrons (b). $T=16$ s, $\alpha=32$, $\varepsilon=0.0$, $\gamma=0.2$, and $\Delta T=0.2$ s.

our two-nephron model for $\alpha=32$, $T=16\,\mathrm{s}$, $\varepsilon=0.0$, and $\gamma=0.2$. Here, we have introduced a slight mismatch $\Delta T=0.2\,\mathrm{s}$ in the delay times between the two nephrons and, as illustrated in Fig. 12(b), the tubular pressure variations follow different trajectories. However, the average period is precisely the same, and the phase difference also remains small. Hence, this is an example of chaotic phase synchronization.

VI. CONCLUSION

One of the fundamental problems in the description of macrophysiological systems is to understand how a group of cells or functional units, each displaying complicated nonlinear dynamic behavior, can interact with one another so as to produce different forms of coordinated function at a higher organizational level.

In the present paper we made a first attempt to establish a model of two interacting nephrons. The interaction was assumed to be brought about either through a hemodynamic coupling or through a vascularly propagated response where signals, initiated by the TGF, travel between the smooth muscle cells from the region close to the macula densa and backwards along the afferent arteriole to the branching point with the arteriole from the neighboring nephron.

The relative strengths of the two coupling mechanisms depends on the structure of the arteriolar network. Where the hemodynamic coupling primarily depends on the length and diameter of the shared interlobular artery in comparison with the lengths and diameters of the separated arterioles, the vascular coupling depends on the propagation distance for the TGF response relative to a characteristic decay length for this response. Because of its instantaneous character, the vascular response tends to produce in-phase synchronization between the neighboring nephrons. The hemodynamic coupling, on the other hand, involves a delay and, hence, tends to produce out-of-phase (or antiphase) synchronization. The result that most of the available experiments show in-phase synchronization is associated with the fact that we have selected nephrons that are situated close to one another. The single example of antiphase synchronization observed so far was obtained for a couple of nephrons that were placed too far from one another for the vascular coupling to be active. The possibility of this type of synchronization was predicted by our model and subsequently found in the experiments.

Since the arteriolar network can be mapped out and the lengths and diameters of the various vessels determined, it is possible to obtain an independent estimate of the typical strength of the hemodynamic coupling and of its variation across the kidney. Similarly, determination of the decay length for the vascularly propagated signal will allow us to estimate the parameter γ of that coupling. Recent investigations have indicated that 60%–70% of all nephrons will be organized in couples or triplets.[29] Moreover, the average lengths of the vascular segments separating neighboring glomeruli have been measured to be 250–300 μm. This is only about 30% of the length that a vascular signal is expected to propagate, suggesting that a large fraction of the nephrons may act in groups rather than as independent functional units.

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