Integrating Microscopic Variability in Systems Modeling

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Variability is a basic property of the physiologic activity from systems function on a macroscopic scale (in both time & size) to channel opening and closing on a microscopic scale. Variability has both deterministic and stochastic components that are represented differentially across biologic scales and modulated continually. At the macroscopic or systems level, neural mechanisms underlying deterministic variability include feedback loops, *e*.*g*. reflexes and coupling of rhythms, but those underlying stochastic variability are undefined. At the microscopic level, neural mechanisms underlying stochastic variability are fluctuations in membrane and synaptic currents due to the random openings of ion channels, neurotransmitter release, diffusion and binding. We seek to understand mechanisms determining variability and hypothesize that stochastic properties of microscopic variability contribute to the expression of macroscopic variability. In a conductance-based network model of respiration, we added stochastic ion-channel gating to neural elements in the network. We report that the altered circuit dynamics and phase durations and increased the coefficient of variation of cycle period depended on the number and location of the channels in the neural circuit. Further, suppressing a tonic excitatory input, prolonged phase duration, decreased breathing frequency and increased breath-to-breath variability.

In experimental studies, we applied brief trains (75 Hz, 150 ms) of vagal nerve stimulation (VNS) to periodically ‘force’ or entrain the respiratory rhythm generated by rat-pup *in situ* perfused preparations. We thought that variability of the breathing pattern would decrease during entrainment. However, even though VNS entrained breathing for periods, variability increased overall. The variability was associated with ‘phase-slips’. From a simplified model of a noisy oscillator, the effect of a forcing function on variability depends on the input gain and its interaction with noise causes phase slips. Thus, we interpreted our findings as that normally the vagal input to the respiratory pattern generator is gated and thus, is at ‘low-gain’ and that noise, *i*.*e*. stochastic, microscopic variability can affect macroscopic variability. Then, we tested the effect of blocking activity in the Kölliker-Fuse nucleus (dorsolateral pons), which has reciprocal connections to the nucleus tractus solitarius (nTS) and which theoretically modulates sensory input to the nTS. In this reduced state, VNS entrained the network for long periods and decreased variability overall.

In summary, modeling and experiments suggest that microscopic variability can affect macroscopic variability of the respiratory cycle and that the KFn regulates respiratory rhythm variability directly by acting on neurons in the respiratory pattern generator and indirectly by a gain-control mechanism.

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