a recently discovered negative transcription factor with unusual effects on period, timeless, vrille, and par domain protein 1. To understand the actions of this protein, we introduced a new system of ordinary differential equations to model regulatory networks. The model is faithful in the sense that it replicates biological observations. CWO loop-actions elevate CLK-CYC; the transcription of direct targets responds by integrating opposing signals from CWO and CLK-CYC. CWO, a transcriptional repressor of direct targets in one-dimensional in vitro experiments, is actually a transcriptional activator in vivo. Loop regulation and integration of opposite transcriptional signals appear to be central mechanisms as they also explain paradoxical effects of period gain-of-function and null mutations.

3843-Pos

Cellular Dynamics of Embryomas within Adult Neoplasms

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During vertebrate life, a single cell will contain a single genome until cell death. This genome contains some genes for embryonic development, some genes for adult expression, and other genes which are used both in embryonic life and in adult life. Embryonic-exclusive genes are exquistively selected for complicated expression during organ formation before birth, and are under close supervision by embryonic regulator proteins and RNAs. After birth, the embryonic-exclusive genes are no longer needed, but they are retained in the inactive form within the cell until cell death. The embryonic regulator proteins and RNAs are then replaced by adult regulator proteins and RNAs. Thus, within the adult cell, the inactive embryonic-exclusive genes are left without embryonic regulator proteins and RNAs. In this open state, such embryonic-exclusive genes may again become active. The activation of as little as one embryo-exclusive gene within an adult cell is capable of initiating a new neoplasm within that cell. Such neoplasms are termed embryomas, and as they divide and recruit other embryonic genes to regain similar activity, the new neoplasm will progress to kill the host animal. The dynamics of such embryoma activation and progression is often as explosive, cumulative, and destructive as an avalanche in character. Recently it has been found that providing the missing embryonic regulatory micro RNAs, either *in vitro* or in *vivo*, will reduce the activity of such embryomas, without apparent toxic effects on the subject. Taulli R, Bersani F, Foglizzo V, Linari A, Vigna E, Ladanyi M, Tuschl T, and Ponzetto C, ''The muscle-specific microRNA miR-206 blocks human rhabdomyosarcoma growth in xenotransplanted mice by promoting myogenic differentiation'', J. Clin. Investigation. 119: (8), 2366-2378 (Aug. 2009).
http://www.embryomas.net

3844-Pos

Analytic Parameter Fitting in Stochastic Stem Cell Models

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Pluripotent stem cells produce all of the body's diverse cell types though lineages of cell division and differentiation. One goal of current stem cell research is to create predictive models of cell development hierarchies to validate our understanding of these hierarchies and to guide the design of artificial lineages to produce specific cell types for medical purposes. Stochastic models have been used to study stem cell lineages for nearly 50 years, but a continuing challenge is how to fit the parameters of complex models to noisy experimental cell population data. We have developed a technique that addresses this problem by creating algorithms to automatically generate exact analytical expressions for the probability distributions of different cell types at each successive generation as a function of the model parameters. These expressions can be used with conventional optimizers to find the best-fit model parameters. Although the analytic expressions grow exponentially for complex differentiation hierarchies, the resulting equations are manageable out to the number of generations typically used in experiments. We have tested our parameter fitting strategy using, as ''experimental'' data, Monte Carlo simulations of a three-parameter stochastic model we have developed for T-cell formation from lymphocyte progenitor cells. We organized the Monte Carlo results to mimic two possible experimental protocols. One mimicked replicate measurements of cell differentiation starting with single stems cells, and the other mimicked measurements starting with pooled groups of cells. Our approach yielded good convergence to the stochastic model parameters, even for relatively small numbers of starting cells, showing that this should be practical for fitting models to experimental data. Additionally, our results show that data from replicate single cell experiments allow more reliable model fitting than pooled experiments using the same number of initial stem cells.

3845-Pos

The Oscillatory Rhythmic Activity of Retinal Ganglion Cell Spikes Might Be Induced by Slow Wave Component in *rd1* Mice Retina

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The abnormal rhythmic activities with ~10 Hz frequency were reported not only from field potential (slow wave component) but also from spontaneous spikes of retinal ganglion cells (RGCs) in *rd1* mice. However, there have been only a few studies on the electrically stimulated RGCs of *rd1* mice, and none of them have mentioned the effect of the abnormal rhythmic activity. Therefore, in this study we focused on the mechanism of oscillatory rhythm in RGC spikes to clarify if RGC responses are well evoked with the current stimulus even with this aberrant rhythm. Extracellular recording of *in vitro* retina was performed using 8x8 multi-electrode array (MEA).Biphasic current pulse trains were applied to one channel of MEA and neural activities of RGCs were recorded from the other channels of MEA. The raw waveforms were separated into field potentials and spike train waveforms using low- and high-pass filtering. Typical RGC responses to current stimulus showed multiple peaks with inter-peak intervals of ~100 ms in PSTH. When treated with CNQX + AP7 or strychnine or SCH23390, the frequency of oscillatory rhythm in RGC spikes decreased from ~10 Hz to ~5 Hz. While neither picrotoxin nor gap junction blockers affected the frequency of oscillatory rhythm. All the blockers showed exactly same effects on the oscillatory rhythm in field potential with that in RGC spikes. This strongly suggests that slow wave component might induce the oscillatory rhythm of RGC spikes. With current amplitude modulation from 2-60 uA, the numbers of evoked RGC spikes increased as a function of pulse amplitude, which means that RGC responses are well evoked with current stimulus even with aberrant oscillatory rhythm in *rd1* mice.

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3846-Pos

An Accelerated Algorithm for Stochastic Simulation of Reaction-Diffusion Systems using Gradient-Based Diffusion and Unified Tau-Leaping

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Stochastic simulation of reaction-diffusion systems enables the investigation of stochastic events arising from the small numbers and heterogeneous distribution of molecular species in biological cells. Stochastic variations in intracellular microdomains and in diffusional gradients that are especially prominent in neurites with elongated morphology play a significant part in the spatiotemporal activity and behavior of cells. Although an exact stochastic simulation that simulates every individual reaction and diffusion event occurring in the system gives a most accurate trajectory of the system's state over time, it can be too slow for many practical applications. We present an accelerated algorithm for discrete stochastic simulation of reaction-diffusion systems designed to improve the speed of simulation by reducing the number of time steps required to complete a simulation run. Our method is unique in that it employs two strategies that have not been incorporated in existing spatial stochastic simulation algorithms. First, we treat diffusive transfers between neighboring subvolumes based on concentration gradients. Our treatment necessitates sampling of only the net or observed diffusion events from higher to lower concentration gradients rather than sampling all diffusion events regardless of local concentration gradients. Second, we extend the non-negative Poisson tau-leaping method that was originally developed for speeding up non-spatial or homogeneous stochastic simulation algorithms. Our method calculates each leap time in a unified step for both reaction and diffusion processes while satisfying the leap condition that the propensities do not change appreciably during the leap and ensuring that leaping does not cause molecular populations to become negative. We also present numerical results that illustrate the improvement in simulation speed achieved by incorporating these two new strategies.