Modeling spatial effects in carcinogenesis: Stochastic and deterministic reaction-diffusion

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***Short Abstract* — Models of carcinogenesis lead to models exhibiting diffusion-driven (Turing) instability, but consisting of a single reaction-diffusion equation coupled with a system of ordinary differential equations (ODE). Such models are very different from the classical Turing-type models in that they exhibit qualitatively new patterns of behavior of solutions, including, in some cases, a strong dependence of the emerging pattern on initial conditions and quasi-stability followed by rapid growth of solutions, which may take the form of isolated spikes, corresponding to discrete foci of proliferation. However, the process of diffusion of growth factor molecules is by its nature a stochastic random walk. An interesting question emerges to what extent the dynamics of the deterministic diffusion model approximates the stochastic process generated by the model. We address this question using simulations with a new software tool called sbioPN (spatial biological Petri Nets).**

***Keywords* — cancer modelling, deterministic, stochastic, reaction-diffusion equations, pattern formation, spike solutions.**

I. Model of Early Carcinogenesis

THE model we focus on is based on the following hypotheses: (i) Pre-cancerous cells with concentration $c(x,t)$ in a spatial domain, proliferate at a rate $a(b,c)$, which is enhanced in a paracrine manner by a growth factor $b(x,t)$ bound to cells (ii) Cells are supplied at a rate μ by mutation of normal cells. (iii) Free growth factor $g(x,t)$ is secreted by the cells at the rate $\kappa(c)$, then it diffuses with constant $1/\gamma$, and binds to cell membrane at a rate $\alpha(c)$, becoming the bound factor $b(x,t)$. It then dissociates at a rate d. (iv) Free and bound growth factor particles decay at rates d_g and d_b. Mathematically [1, 2, 3, 4]:

$$\partial c/\partial t = (a(b,c) - d_c)c + \mu$$
$$\partial b/\partial t = \alpha(c)g - d_b b - db$$
$$\partial g/\partial t = \gamma^{-1}\Delta_x g - \alpha(c)g - d_g g + db + \kappa(c)$$

with homogeneous Neumann boundary conditions $\partial_x g(x,t)_{|x\in\Gamma} = 0$

II. Deterministic versus Stochastic Dynamics

We considered the stochastic extension of a one dimensional reaction-diffusion model of early carcinogenesis that exhibits Turing instabilities in its deterministic formulation. The stochastic spatial system shows an effect by which, when averaged over a large number of realizations, the initial levels of the spikes generated by the corresponding deterministic system, exhibit in all cases a sudden drop in spike levels. In addition, the mathematically intriguing behavior of the deterministic model with spatial effects is partly destroyed when stochastic effects are added (Figure).

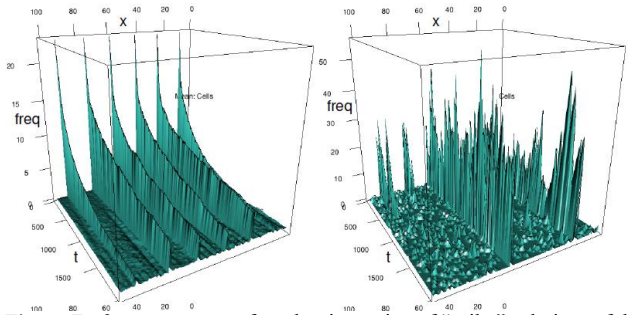

Figure Evolution in time t of stochastic version of "spiky" solutions of the system of reaction-diffusion and ordinary DEs. *Left:* Average of 1000 realization, qualitatively similar but not identical with the deterministic version (not shown). *Right* Single realization of the random process.

III. Conclusion

Much of spatial modeling in biology has been accomplished using partial differential equations without reference to stochasticity. In the system considered by us, continuity and diffusion act to produce asymptotically irregular (spiky) solutions. The stochastic version of the system, at the single realization level, preserves enough spikeness to be a model of spontaneous formation of early cancer foci. However, spikes are now frequently reversible: with new ones appearing and old ones vanishing. The picture is qualitatively different from that in the deterministic reaction-diffusion model.

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