Parallel Session

Physiology II

MODELLING ANTI-INFLAMMATORY SYSTEMS – SPATIAL CONSIDERATIONS IN THE RESOLUTION OF INFLAMMATION

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Keywords: Inflammation, Partial Differential Equations, Resolution, Spatial models.

There is growing interest in inflammation due to its involvement in myriad medical conditions. Recent investigations show that inflammation is actively controlled by anti-inflammatory processes that can be modulated therapeutically. Accordingly, the mechanisms that resolve inflammation are of great interest, the interactions between macrophages and neutrophil-mediated pro-inflammatory processes in particular.

Existing mathematical models describing macrophage-neutrophil interactions are limited by their design, which generally takes the approach of spatially averaging biological quantities across the affected tissue. Assuming spatial homogeneity becomes increasingly spurious as the spatial scale of the damage increases, with clusters of neutrophils causing significant local tissue damage, while inflammation may resolve elsewhere. Furthermore, recent evidence points to aspects of the inflammatory response being modified under aging and trauma, with changes in e.g. directed neutrophil motility and the macrophage functional response potentially influencing long-term outcomes.

We extend an existing ordinary differential equations (ODE) model to incorporate spatial information regarding inflammatory mediators and immune cells. We analyse the resulting partial differential equation model's solutions, illustrating that the model admits spatially inhomogeneous solutions (steady states and sustained oscillations) that the corresponding ODE model neglects. We examine the impact of changes to key biological mechanisms, in terms of permissible solutions, with a view to simulating new therapeutic interventions.

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MODELLING CORNEAL EPITHELIUM MAINTENANCE AND RECOVERY

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Keywords: Ordinary differential equations, Stochastic model, Partial differential equations, Limbal stem cells.

The cornea is the clear shield that covers the eye, estimated to contribute approximately two thirds of the eye's optical power. Therefore, cornea protection is highly important for vision and is achieved by maintaining its outermost layer, the corneal epithelium. Corneal epithelium maintenance depends on a peripheral population of stem cells, known as limbal stem cells, that continuously replenish the basal epithelium layer through generating transient amplifying cells (TAC). TACs move from the periphery to the centre, undergoing several rounds of cell division, before terminal differentiation (TD). TD cells lose contact with the basal layer and move up through the epithelium until they are eventually shed at the surface. We present a mathematical model based on an analogy to chemical reactions aiming to: (i) clarify the main factors involved in the maintaining process; (ii) determine the constraints placed on the proliferation process for healthy maintenance; (iii) investigate robustness via noise analysis. We extend to a spatial model, investigating the mechanisms that account for transient amplifying cell redistribution from the periphery to the centre. To investigate dynamics following wound or disease type scenarios, we further investigate recovery following perturbations to the cornea.

References

[1] Moraki E, Grima R and Painter KJ. (2018). *A stochastic model of corneal epithelium maintenance and recovery following perturbation*. Submitted.

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THE INFLUENCE OF TRANSPORT PROTEINS AND COMPETING STEROIDS ON THE PLASMA CORTISOL DYNAMICS

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Keywords: Cortisol, Corticosteroid-Binding Globulin, Hypothalamic-Pituitary-Adrenal Axis, Oscillations, Mechanism based modelling.

In the blood the greater part of the steroid hormone cortisol is found bound to the transport proteins corticosteroid-binding globulin (CBG,$\sim$ 70%) and albumin ($\sim$ 20%), while only approximately 10% is on free form. Only free cortisol is considered bioactive. The methods for making direct measurements of free cortisol are both time-consuming and labour-intensive. Hence, in most clinical procedures only the total concentration of cortisol is measured and the free cortisol concentration is estimated afterwards.

In a recent paper [1] by non-linear mechanism based modelling we investigate the influence of the transport proteins, the CBG-cleaving enzyme neutrophil elastase and competition from the two steroids progesterone and testosterone on the plasma cortisol distribution in blood. Using equilibrium assumptions we obtain a static version of the model that serves as a new method for calculating plasma free cortisol. Some of the terms of the model equations are much smaller than others and can be ignored without changing the model predictions considerably. Hereby a fourth order polynomial equation is obtained. Only one physiologically relevant solution exists and can, accordingly, serve as a new and improved formula for calculating the plasma free cortisol concentration [1].

In earlier equilibrium models [2, 3, 4] competition from other steroids in binding to CBG was left out. Our modelling work shows that while testosterone does not influence free cortisol concentration, progesterone does both under high level circumstances as seen in pregnancy and during the normal menstrual cycle of women.

The enzyme neutrophil elastase cleaves CBG and thereby decreases CBG's affinity for cortisol. The concentration of elastase and the kinetic constants describing the activity of elastase are collected in one single input parameter in the model. Sensitivity analysis shows that the model is very sensitive towards this parameter. The model fits data excellently, when the elastase activity is treated subject specific, and still performs better than earlier equilibrium models [2, 3, 4], when it is fitted collectively for more subjects. Furthermore,

model comparison shows that the models [2, 3, 4, 1] differ considerably in their predictions for cortisol distribution on different forms, i.e. free cortisol and cortisol bound to albumin, intact CBG and elastase-cleaved CBG.

However, the level of cortisol in the blood is highly dynamic. A circadian rhythm interacts with faster, so-called ultradian, oscillations. In data of the level of CBG an approximately opposite circadian rhythm is seen. In the article [5] a mechanism based non-linear ordinary differential equations model of the neuroendocrine system the Hypothalamic-Pituitary-Adrenal axis controlling the cortisol level with CBG included is stated. We compare the model outcome to data and investigate the influence of CBG on the shape of the ultradian oscillations.

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References

[1] J. Gudmand-Hoeyer, J. T. Ottesen. (2018). *Analysis and validation of a new extended method for estimating plasma free cortisol including neutrophil elastase and competition from other steroids*, Manuscript submitted for publication.

[2] J.-L. Coolens, H. van Baelen, W. Heyns.(1987). *Clinical use of unbound plasma cortisol as calculated from total cortisol and corticosteroid-binding globulin*, J. Steroid Biochem. 26 (2), 197–202.

[3] R. I. Dorin, H. K. Pai, J. T. Ho, J. G. Lewis, D. J. Torpy, F. K. Urban, C. R. Qualls. (2009). *Validation of a simple method of estimating plasma free cortisol: role of cortisol binding to albumin*, Clin. Biochem. 42, 64–71.

[4] P. T. T. Nguyen, J. G. Lewis, J. Sneyd, R. S. F. Lee, D. J. Torpy, P. R. Shorten. (2014). *Development of a formula for estimating plasma free cortisol concentration from a measured total cortisol concentration when elastase-cleaved and intact corticosteroid binding globulin coexist*, J. Steroid Biochem. Mol. Biol. 141, 16–25.

[5] J. Gudmand-Hoeyer, J. T. Ottesen. (2018). *Binding of cortisol in blood magnifies diurnal variations in ultradian amplitudes with impact on clinical measurements*, Manuscript submitted for publication.

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MATHEMATICAL MODEL OF FLUID AND CO_2 TRANSPORT ACROSS THE RETINAL PIGMENT EPITHELIUM

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Keywords: Tetinal pigment epithelium, Osmosis, Electroosmosis, Ion transport.

The retinal pigment epithelium (RPE) is the outermost cell layer of the retina that separates the photoreceptors from Bruch's membrane and the choroidal blood supply. It has several important physiological functions, among which is removal of excess fluid and CO_2 from the sub-retinal space into the choroid. Fluid transport across the RPE is reguated by the epithelial pumping, failure of which leads to fluid accumulation in the subretinal space and is closely associated with several pathological conditions, such as age-related macular degeneration, macular edema and retinal detachment. Failure to remove CO_2 results in acidosis, which inhibits retinal function [1]. Identifying and quantifying the mechanisms that are responsible for this transport can suggest strategies to prevent or treat fluid and CO_2 accumulation.

In this work we develop a mathematical model that couples fluid, ion and CO_2 transport across the RPE. We consider two possible mechanisms that drive fluid flow: osmosis and electroosmosis. Osmosis is induced by jumps in ion concentrations across cell membranes. This means that one needs to model ion transport to get the concentration distribution in the tissue. We consider the presence of following species: Na^+, K^+, Cl^-, HCO_3^-, H^+, CO_2 and H_2CO_3 and model their transport across the cell layer with Nernst-Plank equations coupled with Poisson equation for the electrical potential. We also account for possible reactions between the species. Electro-osmotic flow can occur in the cleft gap between adjacent cells. To model it one needs to resolve the electrical double layers at the lateral walls of the cell.

The model calculates the water fluxes across the RPE, the distribution of concentrations of different species, the electrical potential and CO_2 flux. Moreover, it predicts that the spatial variability of ion concentrations along the cleft gap osmotically drives flow across the lateral cell membranes. This flow is directed from the sub-retinal space to the choroid and its magnitude is comparabe to measured values. Electroosmosis has very little effect on

the flow, as it is two orders of magnitude smaller than osmosis and has an opposite direction. This suggests that local osmosis is the main driving mechanism for water transport across the RPE.

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References

[1] Adijanto, J.; Banzon, T.; Jalickee, S.; Wang, N. S. & Miller, S. S. CO2-induced ion and fluid transport in human retinal pigment epithelium *J. Gen. Physiol.*, 2009, 133, 603-622

Parallel Session

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MATHEMATICAL MODELLING OF THE TENDON HEALING PROCESS: BLOW-UPS MEAN HEALING

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Keywords: Collagen remodelling, Blow-ups, Integro-differential equations, Tendon healing.

Tendon injuries, although not directly threatening the lives of the individual affected, can still significantly lower their quality of life. For a long time, the main therapeutic approach was surgery followed by an arduous rehabilitation. However, even after a year the structure and function of the injured tendon remains inferior to the healthy one. Only recently with new advances in regenerative medicine have new therapeutic methods become available. Nonetheless, better use of these methods requires a deeper understanding of the healing process itself, which is multi-scale, complex and not fully understood. We present a novel modelling approach to tendon healing, consisting of a new integro-differential equation model which describes collagen remodelling during the tendon healing process. From the analysis of the model, we relate the possible blow-up of solutions with the healing of injury without scar formation. Possible extensions of the model are also discussed.

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References

[1] G. Dudziuk, M. Lachowicz, H. Leszczyński, Z. Szymańska, 2018. *A Simple Model of Collagen Remodelling*, Discrete and Continuous Dynamical Systems - B, submitted.