Mac Gabhann Rotation

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1 The Model

The model is implemented in matlab as a system of 21 ordinary differential equations with 60 parameters per compartment. We assume the presence of a main body, blood, and primary tumor compartment and the transport of molecules between them via bi-directional permeability and lymphatic drainage. The addition of metastatic compartments are possible in the current framework. The moleuclar reactions included in the model are described below.

Matrix Binding

$$\begin{aligned}
\mathrm{VEGF_{165}} + \mathrm{M_{ECM}} &\rightleftharpoons \mathrm{M_{ECM}VEGF_{165}} \\
\mathrm{VEGF_{165}} + \mathrm{M_{EBM}} &\rightleftharpoons \mathrm{M_{EBM}VEGF_{165}} \\
\mathrm{VEGF_{165}} + \mathrm{M_{PBM}} &\rightleftharpoons \mathrm{M_{PBM}VEGF_{165}}
\end{aligned}$$

Primary VEGF Binding

$$\begin{aligned}
\mathrm{VEGF_{165}} + \mathrm{R_1} &\rightleftharpoons \mathrm{R_1VEGF_{165}} \\
\mathrm{VEGF_{165}} + \mathrm{R_2} &\rightleftharpoons \mathrm{R_2VEGF_{165}} \\
\mathrm{VEGF_{165}} + \mathrm{N_1} &\rightleftharpoons \mathrm{N_1VEGF_{165}} \\
\mathrm{VEGF_{165}} + \mathrm{N_2} &\rightleftharpoons \mathrm{N_2VEGF_{165}}
\end{aligned}$$

Ternary Binding

$$\begin{aligned}
\mathrm{VEGF_{165}N_1} + \mathrm{R_2} &\rightleftharpoons \mathrm{R_2VEGF_{165}N_1} \\
\mathrm{VEGF_{165}R_2} + \mathrm{N_1} &\rightleftharpoons \mathrm{R_2VEGF_{165}N_1} \\
\mathrm{VEGF_{165}N_2} + \mathrm{R_2} &\rightleftharpoons \mathrm{R_2VEGF_{165}N_2} \\
\mathrm{VEGF_{165}R_2} + \mathrm{N_2} &\rightleftharpoons \mathrm{R_2VEGF_{165}N_2}
\end{aligned}$$

Receptor Coupling

$$\mathrm{R}_1 + \mathrm{N}_1 \rightleftharpoons \mathrm{R}_1\mathrm{N}_1$$
$$\mathrm{R}_1 + \mathrm{N}_2 \rightleftharpoons \mathrm{R}_1\mathrm{N}_2$$

Note: VEGF_{165} doesn't bind to either coupled receptor but VEGF_{121} does.

MVR reactions

$$\mathrm{M}_{\mathrm{EBM}}\mathrm{VEGF}_{165} + \mathrm{R}_1 \rightleftharpoons \mathrm{M}_{\mathrm{EBM}}\mathrm{VEGF}_{165}\mathrm{R}_1$$
$$\mathrm{R}_1\mathrm{VEGF}_{165} + \mathrm{M}_{\mathrm{EBM}} \rightleftharpoons \mathrm{M}_{\mathrm{EBM}}\mathrm{VEGF}_{165}\mathrm{R}_1$$
$$\mathrm{M}_{\mathrm{EBM}}\mathrm{VEGF}_{165} + \mathrm{R}_2 \rightleftharpoons \mathrm{M}_{\mathrm{EBM}}\mathrm{VEGF}_{165}\mathrm{R}_2$$
$$\mathrm{R}_2\mathrm{VEGF}_{165} + \mathrm{M}_{\mathrm{EBM}} \rightleftharpoons \mathrm{M}_{\mathrm{EBM}}\mathrm{VEGF}_{165}\mathrm{R}_2$$

1.1 Model Parameters

Table 1: General Model Parameters

parameter	Description	Tissue Specific?	Units
k_{on}	binding rates for molecular reactions	no[1]	$M^{-1}s^{-1}$ or $\frac{moles}{cm^2}^{-1}s^{-1}$
k_c	receptor coupling rates	no[1]	$\frac{moles}{cm^2}^{-1}s^{-1}$
k_{off}	off-binding rates for molecular reactions	no	s^{-1}
q_x	constant secretion of x	yes	$\frac{moles}{cm^3}$
k_L	lymphatic drainage	yes	cm^3/s
k_p	bi-directional vascular permeability	yes	cm/s
S_{jB}	total abluminal EC surface area	yes	cm^2
γ	endothelial cell surface recruitment factor	no	-
K_{AV}	fraction of volume available	yes	-
U	tissue volume	yes	cm^3
k_{CL}	clearance from blood	no	s^{-1}
k_{prod}	production rate for free receptors delivered to cell surface	**?**	$\frac{moles}{cm^2\mathrm{tissue}}$
k_{int}	Receptor internalization, ligand independent	no	s^{-1}
k_{deg}	Receptor degradation, ligand independent	no	s^{-1}
f	Fraction of EBM accessible to cell surface receptors	yes	-
ESAV	Endothelial surface area to volume ratio	yes	$\mathrm{cm}^2/cm^3 tissue$
ECSA	Endothelial cross sectional surface area	yes	cm^2/EC

[1] Units must be converted with tissue-specific parameters.

Note that k_{on} needs to be converted to a biologically relevant quantity by on of the following,

$$k_{on} \text{ in } \frac{moles}{cm^3 tissue}^{-1} \cdot s^{-1} = k_{on} \text{ in } M^{-1}s^{-1} \cdot \frac{1000}{\text{available IF volume fraction for a particular tissue}}$$

$$k_{on} \text{ in } \frac{moles}{cm^3 tissue}^{-1} \cdot s^{-1} = k_{on} \text{ in } \frac{moles}{cm^2 SA}^{-1} \cdot s^{-1} \cdot \frac{1}{ESAV}.$$

Most parameters were taken from Lindsay's 2017 paper unless otherwise noted in the code (Clegg and Mac Gabhann, 2017). Those that weren't taken from Lindsay's paper were taken from (Bender and Mac Gabhann, 2015; Gabhann and Popel, 2006; Konyalioglu et al., 2015; Stefanini et al., 2010).

1.2 Assumptions

1. We assume that rate of permeability, lymphatic drainage, and clearance from blood is the same for all molecules since they are similar in size.
2. We assume that bi-directional permeability constant is the same in both directions.
3. We assume that most parameters are the same for N1 and N2 except for those reported in the Bender 2015 paper.
4. The current model assumes that VEGF_{165} secretion is the same for all compartments.

1.3 Limitations

1. The current model only includes VEGF_{165}
2. There is no binding to tumor cells

2 Outline for Next Steps

2.1 Parameterizing the model with real data

In Joe's 2105 paper, he simulated patient-specific concentration profiles by altering the secretion rate of tumor cells only (Bender and Mac Gabhann, 2015). Specifically, the log2-transformed gene expression data were median-centered and added to the log2-transformed nominal secretion rates. We can accomplish this in our model by collecting VEGF_{165} gene expression data from primary and metastatic tumors and repeating Joe's process. Look to first supplemental file of Joe's paper to see the details of which data sets he used.

2.2 Simulating stochastic appearance of metastases

Preliminary work has only included simulations without metastastasis compartments. However, the code is written such that compartments can be added easily. Simply adjusting the argument to `declareParams_multi_tissue_VEGF(n_met)` will introduce additional metastasis compartments with the same parameters as the primary tumor. This function will need to be edited if the user wishes to specify unique parameters for metastasis compartments.

Once metastasis compartments have been parameterized as desired, the next step is to simulate their stochastic appearance. The github repo includes psuedo code with a framework for one way to do so. In summary, the model is simulated for a set amount of time with no metastasis. Then, a stochastic process determines if a new metastasis has formed. If not, then the simulation continues for another pre-determined duration with the same parameters, using the end of the prior simulation as an initial condition. If a metastasis has formed, then the model parameters are updated using `declareParams_multi_tissue_VEGF(n_met)`. The initial condition is a combination of the state of the system from the prior simulation plus zeros for the new metastasis compartment. The updated model is then run for a set duration until it is time to determine if a new metastasis has formed and repeat the process.

At the end of the total simulation duration, there is some formatting required to collect results from each segment since they are generated from models with different numbers of compartments.

Alternatively, the model can be run from the beginning with the maximum number of metastases included in the model but parameters for all metastasis compartments set to 0. This method is probably simpler because then the formation of a new metastasis just corresponds to altering the parameters for that compartment and continuing the simulation - no reformatting needed. The model would have I have not written pseudo code for this approach.

References

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