

Supplemental Material to:

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**Animal models of enteroaggregative *Escherichia coli*
infection**

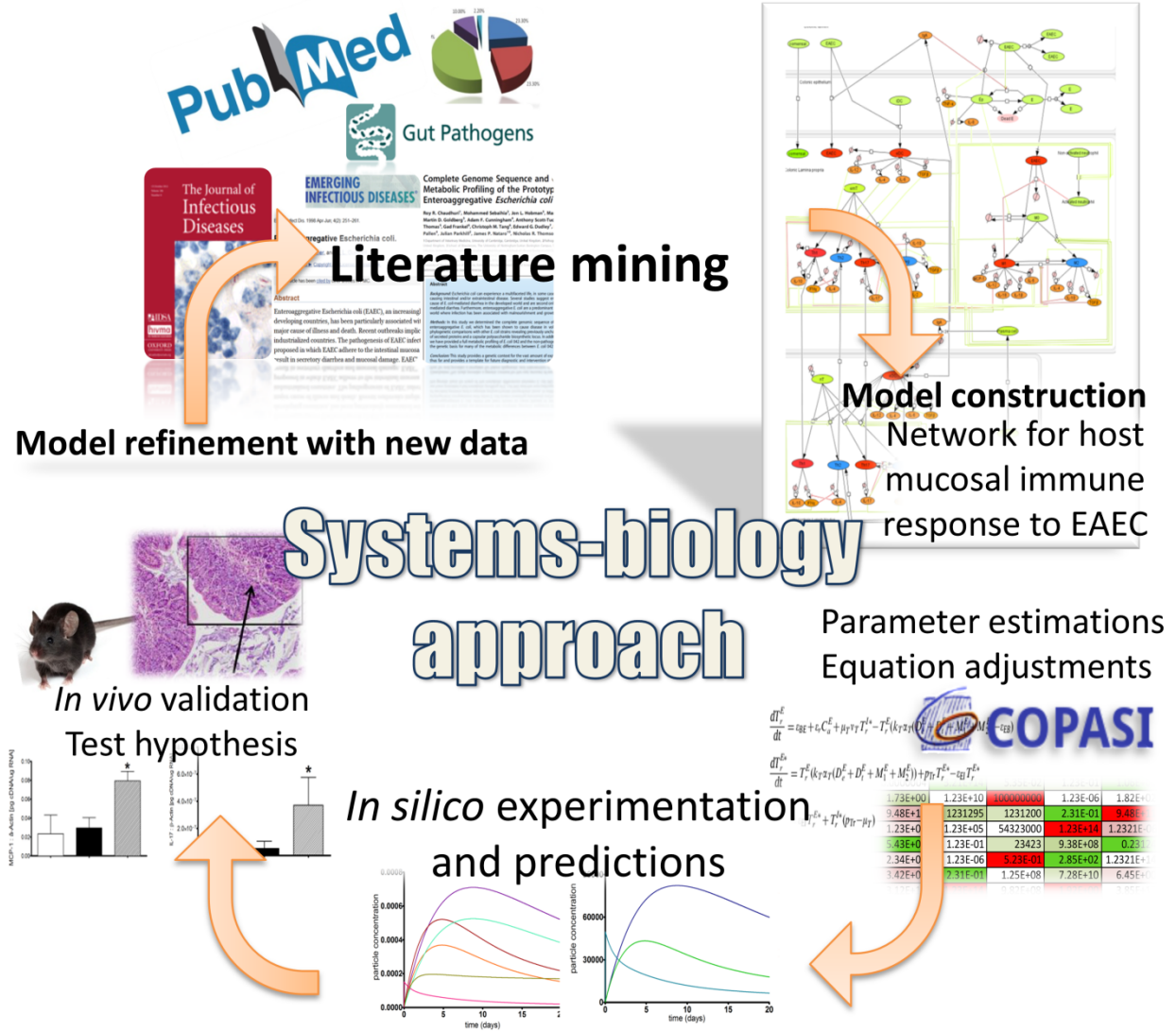
Gut Microbes 2013; 4(4)

<http://dx.doi.org/10.4161/gmic.24826>

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Animal Models of Enteroaggregative *Escherichia coli* Infection

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Supplementary Figure 1: The process of a systems biology approach to study host response to enteroaggregative *Escherichia coli* (EAEC). The systems biology approach used to develop, test, and refine computational models is a cyclical process that incorporates data from multiple

disciplines to provide a more holistic overview of host responses to pathogen. In depth literature mining for qualitative and quantitative data lays the foundation for known mechanisms of host-pathogen interaction. Pathways of interest are incorporated into a visual design using Systems Biology Markup Language (SBML) software. The SBML structure is then fully integrated into a program capable of simulating the dynamic processes in the network such as the COmplex PATHway SIMulator (COPASI) application. The kinetics in the computational model are calibrated using a database of compiled data and *in silico* experimentation takes place to form predictions. Lab experiments are performed to validate computational hypotheses and provide information that promotes re-shaping and re-calibrating the network.

Supplementary Figure 2.

Ordinary differential equations from EAEC T cell differentiation model

$$\begin{aligned} \frac{d([Treg])}{dt} &= -V_{colon} \cdot (K1_{(re17)} \cdot [Treg]) \\ &\quad + ([emT] \cdot (K1_{(re21)} \cdot [TGF\beta] + K2_{(re21)} \cdot [IL10])) \\ &\quad + V_{colon} \cdot ([nt] \cdot (K1_{(re7)}) \cdot [EAEC]) \\ \frac{d([Th17])}{dt} &= -V_{colon} \cdot (K1_{(re16)} \cdot [Th17]) \\ &\quad + ([emT] \cdot (K1_{(re9)} \cdot [IL6] + K2_{(re9)} \cdot [TGF\beta] + K3_{(re9)} \cdot [IL17])) \\ &\quad + V_{colon} \cdot ([nt] \cdot K1_{(re7)}) \cdot [EAEC] \\ \frac{d([Th1])}{dt} &= -V_{colon} \cdot (K1_{(re16)} \cdot [Th1]) \\ &\quad + ([emT] \cdot (K1_{(re20)} \cdot [IFN\gamma] + K2_{(re20)} \cdot [TNF\alpha])) \\ &\quad + V_{colon} \cdot ([nt] \cdot K1_{(re8)}) \cdot [EAEC] \\ \frac{d([EAEC])}{dt} &= -V_{colon} \cdot ([EAEC] \cdot K1_{(re22)} \cdot [Th1] + K2_{(re22)} \cdot [Th17]) \\ \frac{d([TNF\alpha])}{dt} &= -V_{colon} \cdot (K1_{(re18)} \cdot [TNF\alpha]) \\ &\quad + V_{colon} \cdot ([pTNF\alpha] \cdot K1_{(re5)}) \cdot [Th1] \\ \frac{d([TGF\beta])}{dt} &= -V_{colon} \cdot (K1_{(re14)} \cdot [TGF\beta]) \\ &\quad + V_{colon} \cdot ([pTGF\beta] \cdot K1_{(re4)}) \cdot [Treg] \\ \frac{d([IL6])}{dt} &= -V_{colon} \cdot (K1_{(re13)} \cdot [IL6]) \\ &\quad + (([pIL6] \cdot K1_{(re19)}) \cdot [Th17] + K2_{(re19)} \cdot [External_Source]) \\ \frac{d([IL17])}{dt} &= -V_{colon} \cdot (K1_{(re12)} \cdot [IL17]) \\ &\quad + V_{colon} \cdot ([pIL17] \cdot K1_{(re3)}) \cdot [Th17] \\ \frac{d([IL10])}{dt} &= -V_{colon} \cdot (K1_{(re11)} \cdot [IL10]) \\ &\quad + V_{colon} \cdot ([pIL17] \cdot K1_{(re2)}) \cdot [Treg] \\ \frac{d([IFN\gamma])}{dt} &= -V_{colon} \cdot (K1_{(re10)} \cdot [IFN\gamma]) \\ &\quad + V_{colon} \cdot ([pIFN\gamma] \cdot K1_{(re1)}) \cdot [Th1] \\ \frac{d([emT])}{dt} &= -([emT] \cdot (K1_{(re20)} \cdot [IFN\gamma] + K2_{(re20)} \cdot [TNF\alpha])) \\ &\quad - ([emT] \cdot (K1_{(re21)} \cdot [TGF\beta] + K2_{(re21)} \cdot [IL10])) \\ &\quad - ([emT] \cdot (K1_{(re9)} \cdot [IL6] + K2_{(re9)} \cdot [TGF\beta] + K3_{(re9)} \cdot [IL17])) \end{aligned}$$

Supplementary Figure 2: Ordinary Differential Equations (ODE) based on mass action used for EAEC T cell differentiation model.

Calibration Data - EAEC T cell Differentiation Model - October 2012											
Normalized Gene Expression Data						Bacterial Load in Feces		T cell populations using Flow Cytometry			
time	Norm-TGFb	Norm-TNFa	Norm-IL6	Norm-IL17	Norm-IL10	time	EAEC quantification	time	IL17 producing Th17	IFNg producing Th1	Regulatory T cells
5	0.205190451	0.374654445	0.820866897	1.878670704	1.44011E-05	3	7123.13	14	90888.75	145422	327199.5
5	0.526565841	0.41259717	0.376248029	0	4.87187E-06	3	8110.87	14	92340	295488	203148
5	0.465335146	1.145038168	1.492019431	0	0.137570238	3	7029.98	14	65667.6	98816.64	86464.56
5	1.073833295	1.051633869	0.60447406	0	0.003045569	3	9648.13	14	38165.85	45002.25	64881.945
5	0.587212221	0.52507837	0.604338843	0	0.829391165	3	6342.8	14	103774.65	42936.39	45900
5	0.35608655	0.17683466	0.870331219	0	0.357856336	3	7262.77	14	65667.6	34765.2	38628
5	1.022087714	0.181407061	0.177892283	0	0.004055527	3	5831.49	14	56359.8	61065.36	31311
5	0.17608563	0.931218883	0.172063406	0	0.016478982	3	8028.2	14	73266.32143	103356.5486	113933.2864
5	0.182206071	2.343260188	0.802139037	0	0.014879453	5	16698.6				
5	0.531096623	2.293428757	3.946280992	0	0.000569899	5	13815.5				
5	2.552926526	1.282007511	1.66380789	0	0.013008361	5	16768.1				
5	1.101705867	1.427343333	0.81500049	0		5	14192.1				
5	0.662198985	1.466108149	2.803837412	1.280517645		5	11000.9				
5	0.579466818	5.813574779	0.339358228			5	10120.7				
5	0.550580086	0.870837084	1.16305796			10	1.02E+04				
5	0.550884582	1.036887225	0.378741353			10	10220				
5	0.822758269	1.697312588	0.661226813			10	9114.777778				
5	0.649684972	3.618982588	2.164318271			10	8178.14				
5	0.749999157	1.268701464	1.781327033			10	6826.2				
5	0.999845357	1.775204201	1.883884461			10	9120.777778				
5	1.043476697	3.076379066	1.732616619								
5	0.995644949	2.062706271	0.950616517								
5	0.754005154	6.915222772	0.326008447								
5	0.832142205	1.220192442									
5	0.783040843	1.473058617									
14	3.323645577	1.271855716	0	0	0.769328586						
14	1.549814541	2.490916045	0	0	5.4518E-05						
14	2.391109205	0.620089052	0	0	0.043069344						
14	1.237172033	0.224655528	0	0	0.010619868						
14	1.631424506	0.527973965	1.467541436	0	1.99672E-05						
14	1.370921409	0.790820185	1.910007298	0	1.91688E-07						
14	1.47675425	0.502008032	2.092050209	0	0.001411834						
14	1.490453095	1.161671479	0	0							
14	1.47003875	1.013559943	0	0							
14		1.38106705	0	0							
14		1.2359496	1.022357617	0							
14		2.354934095	0	0							
14		1.5631716	1.204546864	0							
14		1.551700312	1.415570407	0							
14		0.892955401	1.064278998	0							
14			1.623772618	0							

Supplementary Figure 3: Calibration database used to estimate parameters in the EAEC T cell differentiation model. In house data from malnourished EAEC JM221 infected mice were organized by quantitative gene expression, bacterial shedding, and flow cytometry data¹. These were linked to model species and used as reference points for model calibration.

1. Philipson CW, Bassaganya-Riera J, Viladomiu M, Pedragosa M, Guerrant RL, Roche JK, et al. The role of peroxisome proliferator-activated receptor γ in immune responses to enteroaggregative Escherichia coli infection. PloS one In Press.