
Supplementary material:

Dynamical simulations of biofilm formation using SQUAD

To assign continuous activity values to each component, the detailed quorum sensing network assembled as detailed in the paper using cell designer 3.5.1. can now be used as input for the simulation environment SQUAD (DiCara et al., 2007). Using the machine readable file constructed by cell designer allows the software SQUAD to transform the static network into a continuous dynamical system based on ordinary differential equations. Only the topology and the connectivity (different inputs and outputs of one node) are available as information. The dynamics in the network is approximated accordingly, assuming exponential functions. Specifically, SQUAD Is using the equation

$$\frac{dx_i}{dt} = \frac{-e^{0.5h} + e^{-h(\omega_i)}}{(1 - e^{0.5h})(1 + e^{-h(\omega_i - 0.5)})} - g_i x_i \quad (\text{eq. 1})$$

$$0 \leq x_i \leq 1,$$

which describes the change of activation of node x_i over time (DiCara et al., 2007). This transformation is thus achieved without any detailed information on the kinetics by simplifying generic and integrative assumptions: The original discrete step function is translated into a sigmoid response curve. Its magnitude depends on the following parameters: The function gain (h), weights (ω_i) and the decay (g_i). In the absence of kinetic data, the SQUAD simulation sets default values, i.e. 10 and 1 as default values for gain and decay of the exponential terms. Weighting factors ω_i account for the three different conditions of input (a , b , c) to a network node x_i according to whether there is a combination of activatory and inhibitory input or only one type of these inputs present:

$$\omega_i = \begin{cases} \left(\frac{1 - \sum \alpha_n}{\sum \alpha_n} \right) \left(\frac{\sum \alpha_n x_n^a}{1 + \sum \alpha_n x_n^a} \right) \left(1 - \left(\frac{1 + \sum \beta_m}{\sum \beta_m} \right) \left(\frac{\sum \beta_m x_m^i}{1 + \sum \beta_m x_m^i} \right) \right) & a \\ \left(\frac{1 - \sum \alpha_n}{\sum \alpha_n} \right) \left(\frac{\sum \alpha_n x_n^a}{1 + \sum \alpha_n x_n^a} \right) & b \\ \left(1 - \left(\frac{1 + \sum \beta_m}{\sum \beta_m} \right) \left(\frac{\sum \beta_m x_m^i}{1 + \sum \beta_m x_m^i} \right) \right) & c \end{cases} \quad (\text{eq.2})$$

In the formula given, $\{x_n^a\}$ is the set of activators of a node x_i , $\{x_m^i\}$ represents the set of inhibitors affecting x_i , respectively. Formula a is applied if x_i gets both activatory and stimulatory input of further nodes. This is the case for hub nodes such *SarA*, *rot*, *Agr* (see the network structure, Figure 1 of the paper). For only activatory input b is used (e.g. *AIP*, *AgrA-P*, *AgrC* from the network), c represents solely inhibitory input (e.g. *RsbW*, *SigB*). The interpolation between the on and the off state for any node in the system results in an exponential decaying or bell-like shapes for the activation curves of the signalling nodes. The different steepness and trajectory shapes mirror the resulting complex function of activation and inhibition in each network node (see DiCara et al., 2007 for further details).

Statistical Analysis of significance values of predictions for the gene expression analysis

Overall the comparison with the gene expression data and simulation shows good agreement between prediction and experiment, e.g. there is always experimental support for a predicted quorum sensing response under at least one experimental data set for that condition. Hence, the overall performance of the model is strong enough to actually make with confidence new predictions (see also results part 2, where then mutation experiments and their outcome agreed well with the model).

Moreover, one can notice on the basis of the two different *in silico* biofilm⁺ vs. biofilm⁻ datasets and the different *in vitro* *sarA*⁻, *agrA*⁻ and biofilm datasets, that small changes in the experimental conditions may add to the inconsistent behavior of some nodes. This is shown for scenario C (Biofilm⁺ vs Biofilm⁻), comparing two different simulation settings: Simulation 2 and its settings better model the network, simulation 1 alone is not so successful.

Hence as previously mentioned, with more knowledge about the actual scenario (e.g. growth conditions, nutrient availability, pH) regarding the experimental testing of a specific strain an even higher consistency with the simulation could be achieved, given that the simulation has the capability (see Methods section in paper) to incorporate the variables.

However, even testing the individual experiments and data sets and compare these results to the performance of the model simulations shows significant results. This is summarized in the following Table 1S. The *in silico* datasets for all the three different conditions *AgrA*⁺ vs *AgrA*⁻, *SarA*⁺ vs *SarA*⁻ and Biofilm⁺ vs Biofilm⁻ were compared to the *in vitro* dataset from the SAMMD database and further validated using Chi square test.

Table 1S. Chi-square value for *in vitro* data compared to the *in silico* predictions in three different conditions looking at individual experiments.

Experiment	χ^2 -square value		
	sim1	sim2	sim3
<i>Agr</i> ⁺ vs <i>Agr</i> ⁻	11.4734***	4.6274*	10.24**
<i>SarA</i> ⁺ vs <i>SarA</i> ⁻	4.6274*	7.0877**	3.3206*
	C1sim2	C2sim2	C3sim2
Biofilm ⁺ vs Biofilm ⁻	7.4323**	4.9132*	8.4203**

Significance*= P ≤ 0.05, Significance**= P ≤ 0.01, Significance ***=P ≤ 0.001

Table 2S. Activating/Inhibiting outputs of the different nodes.

Interactions between nodes	Source references	Interactions between nodes	Source references
acetic acid -> cidR	Yang et al. 2005	icaAdbc -> emp	Johnson et al. 2008
Agr -> RNAIII	Novick, 2003	icaAdbc -> eap	Johnson et al. 2008
Agr -> RNAII	Novick, 2003	icaR -l icaAdbc	Cue et al. 2009
Agr -> SaeRS	Novick, 2003	lrgAB -l cidABC	Yang et al. 2005
Agr -> sak	Jin et al. 2004	lytSR -> lrgAB	Bronner et al. 2004
Agr -l SarT	Schmidt et al. 2001	MgrA -> SarX	Ballal et al. 2009
AgrA-P -> agr	Novick, 2003	MgrA -> agr	Ballal et al. 2009
AgrB -> AIP	Novick, 2003	MgrA -> SarZ	Ballal et al. 2009
AgrC -> AgrA-P	Novick, 2003	MgrA -> lrgAB	Ingavale et al. 2003
AgrD -> AIP	Novick, 2003	MgrA -> lytSR	Ingavale et al. 2003
AIP -> AgrC	Novick, 2003	MgrA -> arlRS	Ingavale et al. 2003
ArlR-P -> SarA	Fournier, 2001	MgrA -l lytM	Ingavale et al. 2003
ArlR-P -l agr	Fournier, 2001	MgrA -l lytN	Ingavale et al. 2003
ArlR-P -l norA	Fournier et al. 2000	MgrA -l SarV	Ballal et al. 2009
ArlR-P -l sspB	Fournier, 2001	MgrA -l norB	Truong-Bolduc et al. 2006
ArlR-P -l sspA	Fournier, 2001	MgrA -l norC	Truong-Bolduc et al. 2006
ArlR-P -l SplA-F	Fournier, 2001	MgrA -l tet38	Truong-Bolduc et al. 2006
ArlR-P -l hla	Fournier, 2001	msa -> SarA	Sambanthamoorthy et al. 2006
ArlR-P -l hlb	Fournier, 2001	msrR -l SarA	Rossi et al. 2003
arlRS -> ArlS	Fournier, 2001	norG -> norB	Truong-Bolduc and Hooper, 2007
arlRS -> ArlR	Fournier, 2001	norG -l abcA	Truong-Bolduc and Hooper, 2007
ArlS -> ArlR-P	Fournier, 2001	PIA -> biofilm	Boles and Horswill, 2008
Aur -> sspA	Nickerson et al. 2007	rbf -l icaR	Cue et al. 2009
Aur -> biofilm	Boles and Horswill, 2008	RNA II -> AgrB	Novick, 2003
Bap -> biofilm	Trotonda et al. 2005	RNA II -> AgrD	Novick, 2003
branched-chain amino acids -> cody	Majerczyk et al. 2008	RNA II -> AgrA	Novick, 2003
Ccpa -> cidABC	Seidl et al. 2008	RNA III -> SaeQ	Novick and Jiang, 2003
Ccpa -> icaAdbc	Seidl et al. 2008	RNA III -> SaeP	Novick and Jiang, 2003
cidABC -> murein hydrolase	Yang et al. 2005	RNA III -> hlb	Bronner et al. 2004
cidABC -> biofilm	Rice et al. 2007	RNA III -> hld	Bronner et al. 2004
cidR -> cidABC	Yang et al. 2005	RNA III -> hla	Fournier, 2001
clfA -> biofilm	Bartlett and Hulten, 2010	RNA III -l Rot	Bronner et al. 2004
clfB -> biofilm	Bartlett and Hulten, 2010	RNA III -l coa	Bronner et al. 2004
ClpXP -> SarS	Cheung et al. 2008	RNA III -l spa	Bronner et al. 2004
Coa -> biofilm	Palma et al. 1999	RNA III -l Sars	Cheung et al. 2008
Cody -> icaAdbc	Majerczyk et al. 2008	RNA III -l biofilm	Boles and Horswill, 2008
Cody -> hla	Majerczyk et al. 2008	Rot -> biofilm	Bronner et al. 2004
Cody -> agr	Majerczyk et al. 2008	Rot -> sdrC	Saïd-Salim et al. 2003
cvfA -> SarZ	Nagata et al. 2008	Rot -> clfB	Saïd-Salim et al. 2003
cvfA -> agr	Nagata et al. 2008	Rot -> SarS	Ballal et al. 2009
cvfB -> agr	Nagata et al. 2008	Rot -> spa	Bronner et al. 2004
cvfB -> spa	Nagata et al. 2008	Rot -l geh	Saïd-Salim et al. 2003
DNAse -l biofilm	Huseby et al. 2010	Rot -l SplA-F	Saïd-Salim et al. 2003
Eap -> biofilm	Johnson et al. 2008	Rot -l aur	Gustafsson and Oscarsson, 2008
Emp -> biofilm	Johnson et al. 2008	Rot -l hlgB	Bronner et al. 2004
fnbA -> biofilm	Boles and Horswill, 2008	Rot -l hlgC	Bronner et al. 2004
fnbB -> biofilm	Boles and Horswill, 2008	Rot -l sspA	Gustafsson and Oscarsson, 2008
Glucose -> acetic acid	Yang et al. 2005	Rot -l sspB	Gustafsson and Oscarsson, 2008
GTP -> cody	Majerczyk et al. 2008	Rot -l sspC	Gustafsson and Oscarsson, 2008
hla -> biofilm	Caiazza and O'Toole, 2003	Rot -l hla	Bronner et al. 2004
hld -l biofilm	Huseby et al. 2010		
sspA -> biofilm	Vuong et al. 2000		
icaAdbc -> PIA	Boles and Horswill, 2008		

Rot -l hlb	Bronner et al. 2004	SarA -l sarT	Schmidt et al. 2001
RsbP -> RsbV	Palma and Cheung, 2001	SarA -l sarV	Ballal et al. 2009
RsbU -> RsbV	Palma and Cheung, 2001	SarA -l sak	Jin et al. 2004
RsbV -l RsbW	Palma and Cheung, 2001	SarR -> agr	Ballal et al. 2009
RsbW -l SigB	Palma and Cheung, 2001	SarR -l SarA	Gustafsson and Oscarsson, 2008
SaeR-P -> SaeQ	Adhikari and Novick, 2008	SarS -> spa	Cheung et al. 2008
SaeR-P -> SaeP	Adhikari and Novick, 2008	SarS -> hla	Cheung et al. 2008
SaeR-P -> hla	Mainiero et al. 2010	SarT -> SarS	Schmidt et al. 2003
SaeR-P -> hlb	Mainiero et al. 2010	SarT -l SarU	Manna and Cheung, 2003
SaeR-P -> spa	Giraudo et al. 1997	SarU -> agr	Schmidt et al. 2001
SaeR-P -> fnbA	Mainiero et al. 2010	SarX -l agr	Ballal et al. 2009
SaeR-P -> hlgB	Rogasch et al. 2006	SarZ -> RNAIII	Ballal et al. 2009
SaeR-P -> hlgC	Rogasch et al. 2006	SarZ -l SarS	Ballal et al. 2009
SaeR-P -> emp	Johnson et al. 2008	sdrC -> biofilm	Bartlett and Hulten, 2010
SaeR-P -> eap	Johnson et al. 2008	SigB -> asp23	Palma et al. 2006
SaeR-P -> coa	Mainiero et al. 2010	SigB -> clfA	Entenza et al. 2005
SaeR-P -> hlgA	Rogasch et al. 2006	SigB -> SarA	Bischoff et al. 2001
SaeR-P-> DNase	Giraudo et al. 1999	SigB -> SarS	Bronner et al. 2004
saeRS -> saeP	Adhikari and Novick, 2008	SigB -> cidABC	Rice et al. 2004
saeRS -> saeQ	Adhikari and Novick, 2008	SigB -> fnbA	Entenza et al. 2005
saeRS -> saeR	Adhikari and Novick, 2008	SigB -l agr	Bischoff et al. 2001
saeRS -> saeS	Adhikari and Novick, 2008	SigB -l lrgAB	Rice et al. 2004
SaeS -> saeR-P	Adhikari and Novick, 2008	SigB -l saeRS	Geiger et al. 2008
sak -l biofilm	Jin et al. 2004	Spa-> biofilm	Boles and Horswill, 2008
SarA -> agr	Fournier, 2001	SplA-F -l biofilm	Boles and Horswill, 2008
SarA -> hlgC	Bronner et al. 2004	sspA -> sspB	Nickerson et al. 2007
SarA -> hlgB	Bronner et al. 2004	sspA -l sspC	Nickerson et al. 2007
SarA -> tsst	Bronner et al. 2004	sspA -l fnbB	Nickerson et al. 2007
SarA -> fnbB	Bronner et al. 2004	sspA -l fnbA	Karlsson et al. 2001
SarA -> fnbA	Bronner et al. 2004	sspA -l biofilm	Boles and Horswill, 2008
SarA -> emp	Johnson et al. 2008	sspA -l spa	Karlsson et al. 2001
SarA -> eap	Johnson et al. 2008	sspB -l biofilm	Boles and Horswill, 2008
SarA -> icaADBC	Trotonda et al. 2005	sspC -l sspB	Nickerson et al. 2007
SarA -> hla	Bronner et al. 2004	walR/K -> isaA	Dubrac et al. 2007
SarA -> SarS	Cheung et al. 2008	walR/K -> atlA	Dubrac et al. 2007
SarA -> Bap	Trotonda et al. 2005	walR/K -> lytM	Dubrac et al. 2007
SarA -l sspC	Gustafsson and Oscarsson, 2008	walR/K -> sceD	Dubrac et al. 2007
SarA -l sspA	Gustafsson and Oscarsson, 2008	walR/K -> ssaA	Dubrac et al. 2007
SarA -l sspB	Gustafsson and Oscarsson, 2008	walR/K -> biofilm	Dubrac et al. 2007
SarA -l aur	Gustafsson and Oscarsson, 2008		

In this table all the nodes of the constructed network are shown. The -> sign shows the activation while the -l shows the inhibition between the nodes.

Table 3S. Microarray meta-analysis.

A)								
node	<u>A1: Cassat [48] agrA OD 1</u>	<u>A1-T1 correlation</u>	<u>agrA up/down sim T1</u>	<u>A2: Cassat [48] agrA OD 3</u>	<u>A2-T3 correlation</u>	<u>agrA up/down sim T3</u>	<u>A3-T3 correlation</u>	<u>A3: Dunman [49] agrA RN27</u>
abcA								
AgrB			+			+		
AgrC				+				+
AgrD			+			+		+
arlR								
arlS								
asp23								
atlA								
aur						+		+
ccpa								
clfA			+					
clfB								+
ClpP								
ClpX								
coa			+					
cody								
fnbA			+			+		
fnbB								
geh			+	+		+		+
hla			+	+		+		+
hlb			+			+		
hld	+		+			+		+
hlgA			+	+		+		
hlgB			+			+		+
hlgC			+			+		+
icaA								
icaB								
icaC								
icaD								
icaR								
isaA								

lrgA								
lrgB								
lytM								
lytN								
lytR								
lytS								
msa								
msrR								
norA								
rbf								
Rot								
RsbU								
RsbV								
RsbW								
SaeR		+			+			
SaeS								
sak		+			+			
SarA								
SarR								
SarS								
SarT								
SarU		+			+			
SarV								
SarX								
SarZ								
sdrC								
SigB								
spa							-	
SplA					+		+	
SplB					+		+	
SplC					+			
SplD					+		+	
SplE					+			
SplF					+		+	
ssaA								
sspA					+			
sspB								
sspC							+	

tsst								
Number of Nodes		70			70		70	
concordant nodes		57			50		56	
non concordant nodes		13			20		14	
nodes with changes in the same direction		1			3		11	
<i>in vitro to in silico consistency in %</i>		81,43			71,43		80,00	

B)								
node	<u>B1: Cassat [48]</u> <u>sarA OD 1</u>	<u>B1-T1</u> <u>correlation</u>	<u>sarA up/down</u> <u>sim T1</u>	<u>B2: Cassat [48]</u> <u>sarA OD 3</u>	<u>B2-T3</u> <u>correlation</u>	<u>sarA up/down</u> <u>sim T3</u>	<u>B3-T3</u> <u>correlation</u>	<u>B3: Dunman</u> <u>[49] agrA RN27</u>
abcA								
AgrA							+	
AgrB			+					+
AgrC								+
AgrD			+					+
arlR								
arlS								
asp23								
atlA							+	
aur	-			-				-
ccpa								
clfA								
clfB								
ClpP								
ClpX								
coa								
cody								
fnbA								
fnbB			+			+		
geh						+		
hla	-					+		+
hlb								
hld						+		+
hlgA								
hlgB			+			+		+
hlgC			+			+		+
icaA			+			+		
icaB			+			+		
icaC			+			+		
icaD			+			+		
icaR								
isaA								
lrgA								
lrgB							-	

lytM							
lytN	-				-		
lytR							
lytS							
msa							
msrR							
norA							
rbf							
Rot							
RsbU							
RsbV							
RsbW							
SaeR					+		
SaeS							
sak	-						
SarR							
SarS							
SarT							
SarU					+		+
SarV							
SarX							
SarZ							
sdrC	-						
SigB							
spa							-
SplA							+
SplB							+
SplC							
SplD							+
SplE							
SplF							
ssaA							
sspA	-				-		+
sspB	-				-		-
sspC	-				-		-
tsst				+		+	

Number of nodes		70			70		70	
concordant nodes		50			53		48	
non concordant nodes		20			17		22	
nodes with changes in the same direction		0			0		4	
<i>in vitro</i> to <i>in silico</i> consistency in %		71,43			75,71		68,57	

C)	<i>Biofilm vs. Planctonic</i>										
	<i>Biofilm Vs Planktonic (SS) Sim. 1</i>	<i>Biofilm Vs Planktonic (AIP) Sim. 2 (compared to Sim 1)</i>	<i>C1-Sim1 correlation</i>	<i>C1-Sim2 correlation</i>	<i>C1 Biofilm Vs Planktonic (maturing) [50]</i>	<i>C2-Sim1 correlation</i>	<i>C2-Sim2 correlation</i>	<i>C2 Biofilm Vs Planktonic 24hr [51]</i>	<i>C3-Sim1 correlation</i>	<i>C3-Sim2 correlation</i>	
abcA											
AgrA											
AgrB	-	-									
AgrC	-										
AgrD	-	-									
arlR											
arlS											
asp23									+		
atlA					+						
aur	-	-									
ccpa											
clfA								+			
clfB	+							+			
ClpP											
ClpX											
coa											
cody											
fnbA		-									
fnbB											
geh	-				+						
hla	-				+						
hlb	-										
hld	-	-									
hlgA	-										
hlgB	-										
hlgC	-										
icaA											
icaB											
icaC								+			
icaD											+
icaR											
isaA											
lrgA											

Number of Nodes			71	71		71	71		71	71		
concordant nodes			41	54		40	51		41	55		
non concordant nodes			30	17		31	20		30	16		
nodes with changes in the same direction			0	0		2			1	1		
<i>in vitro</i> to <i>in silico</i> consistency in %			57,75	76,06		56,34	71,83		57,75	77,46		

¹(A) Three *in vitro* *AgrA*⁺ vs. *AgrA*⁻ scenarios are compared to an *in silico* *AgrA*⁺ vs. *AgrA*⁻ scenario. In (B) three *SarA*⁺ vs. *SarA*⁻ scenarios are compared to an *in silico* *SarA*⁺ vs. *SarA*⁻ scenario. In (C) three *in vitro* biofilm forming vs. not biofilm forming scenarios are compared to two *in silico* biofilm forming vs. no biofilm forming scenarios. The dark green colour in one of the correlation columns means that this node showed no difference between *in vitro* and *in silico*. The dark green colour in one of the correlation columns show similar *in vitro* and *in silico* results. The red colour in one of the correlation columns means that this node did not show the same reaction in the *in vitro* and the *in silico* conditions. “+” indicates that the node is up-regulated three fold in the wild type strain or 2.5 fold in the biofilm forming situation. “-” indicates that this node is up-regulated by the three fold in the mutant strain or by the 2.5 fold in the no biofilm forming situation. A detailed description of the conditions compared can also be found in the Materials and Methods.

Table 4S. Different nodes and their description.

node	Gene Description
abcA	ABC transporter, permease/ATP-binding protein
AgrA	accessory gene regulator protein A (autoinducer sensor protein response regulator protein)
AgrB	accessory gene regulator protein B (putative autoinducer processing protein)
AgrC	accessory gene regulator protein C (autoinducer sensor protein)
AgrD	accessory gene regulator protein D (AIP precursor)
arlR	DNA-binding response regulator ArlR
arlS	sensor histidine kinase ArlS
asp23	alkaline shock protein 23
atlA	bifunctional autolysin
aur	zinc metalloproteinase aureolysin
ccpa	catabolite control protein A
clfA	clumping factor A (fibrinogen and keratin binding surface anchored protein)
clfB	clumping factor B (fibrinogen and keratin binding surface anchored protein)
ClpP	locus for proteolytic subunit ClpP and the Clp ATPase ClpX
ClpX	locus for proteolytic subunit ClpP and the Clp ATPase ClpX
coa	staphylocoagulase precursor
cody	transcription pleiotropic repressor codY
fnbA	fibronectin binding protein A
fnbB	fibronectin binding protein B
geh	glycerol ester hydrolase
hla	alpha-hemolysin
hlb	beta-hemolysin
hld	delta-hemolysin
hlgA	gamma-hemolysin component A
hlgB	gamma-hemolysin component B
hlgC	gamma-hemolysin component C
icaA	intercellular adhesion protein A
icaB	intercellular adhesion protein B
icaC	intercellular adhesion protein C
icaD	intercellular adhesion protein D
icaR	ica operon transcriptional regulator
isaA	immunodominant antigen A
lrgA	holin-like protein LrgA
lrgB	holin-like protein LrgB
lytM	peptidoglycan hydrolase
lytN	cell wall hydrolase
lytR	two-component response regulator lytR
lytS	two-component sensor histidine kinase LytS
msa	hypothetical protein
msrR	peptide methionine sulfoxide reductase regulator MsrR
nora	multi drug resistance protein (norA)
rbf	ribosome-binding factor
Rot	repressor of toxins
RsbU	sigma factor B regulator protein
RsbV	anti-sigma B factor antagonist
RsbW	anti-sigmaB factor
SaeR	DNA-binding response regulator SaeR
SaeS	sensor histidine kinase SaeS

sak	staphylokinase precursor
SarA	staphylococcal accessory regulator A
SarR	staphylococcal accessory regulator R
SarS	staphylococcal accessory regulator S
SarT	staphylococcal accessory regulator T
SarU	staphylococcal accessory regulator U
SarV	staphylococcal accessory regulator V
SarX	staphylococcal accessory regulator X
SarZ	staphylococcal accessory regulator Z
sdrC	Ser-Asp rich fibrinogen-binding, bone sialoprotein-binding protein
SigB	RNA polymerase sigma-B factor
spa	immunoglobulin G binding protein A
SplA	serine protease SplA
SplB	serine protease SplB
SplC	serine protease SplC
SplD	serine protease SplD
SplE	serine protease SplE
SplF	serine protease SplF
ssaA	secretory antigen precursor
sspA	serine protease (V8 protease)
sspB	cysteine protease precursor
sspC	cysteine protease
tssT	toxic shock syndrome toxin-1

Supplementary References

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