**Validation of Core and *Salinispora* models**

**Table S1:** Simulations of Core model under different growth conditions.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|   | **Medium** | **Growth rate** | **Growth rate** | **References** |
|   |  | ***in silico*** | **in vivo** |  |
|   |  | **1/h** |  |  |
| **1** | Medium without Carbon source | 0.000 | no growth | Contador et al 2015 |
| **2** | Medium without Nitrogen source | 0.000 | no growth | Contador et al 2015 |
| **3** | Medium without Sulfur source | 0.000 | no growth | Contador et al 2015 |
| **4** | Medium without Phosphate source | 0.000 | no growth | Contador et al 2015 |
| **5** | Glucose-Minimal Media Anaerobic | 0.000 | no growth | Ahmed et al 2013, Maldonado et al 2005 |
| **6** | Glucose-Minimal Media Aerobic | growth | growth | Ahmed et al 2013, Maldonado et al 2005 |
| **7** | Starch-A1 medium | 0.1346 | growth | This work |
| **8** | ISP2 (glucose-malt-yeast extract agar) | growth |  | Ahmed et al 2013 |
| **9** | ISP5 (glycerol-asparagine agar) | growth |  | Ahmed et al 2013 |
| **10** | ISP4 (inorganic salts-starch agar) | growth |  | Ahmed et al 2013 |
| **11** | ISP3 (oatmeal agar) | growth |  | Ahmed et al 2013 |
| **12** | ISP6 (peptone-yeast extract-iron agar) | growth |  | Ahmed et al 2013 |
| **13** | ISP1 (tryptone yeast extract agar) | growth |  | Ahmed et al 2013 |
| **14** | ISP7 (tyrosine agar) | growth |  | Ahmed et al 2013 |

**Table S2:** Predicted growth rates by iCC926 under different growth conditions.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|   | **Medium** | **Growth rate** | **Growth rate** | **References** |
|   |  | ***in silico*** | **in vivo** |  |
|   |  | **1/h** |  |  |
| **1** | Glucose-Minimal Media | 0.4118 |   | Alam et al 2011 |
| **2** | Glucose-Minimal Media | 0.1489 | growth | Maldonado et al 2005 |
| **3** | Glucose-CM-SS | 0.5714 | 6 (% PCV) | Tsueng et al 2008 |
| **4** | Glucose-CM-SF1 | 0.5533 | 6 (% PCV) | Tsueng et al 2008 |
| **5** | Glucose-CM-SF2 | 0.5533 | growth | Contador et al 2015 |
| **6** | Glucose-CM-not salts | 0.5533 | no growth |  Maldonado et al 2005 |
| **7** | Starch-SS | 0.9342 | growth | Lechner et al 2011 |
| **8** | Starch-SF1 | 0.9160 | +++, 5.97 mg/ml | Tsueng and Lam 2008b; Tsueng and Lam 2010 |
| **9** | Starch-SF2 | 0.9160 | 7.15 mg/ml, 6.45mg/ml | Tsueng and Lam 2008b; Tsueng and Lam 2010 |
| **10** | ISP2 (glucose-malt-yeast extract agar) | 1.288 | +++ | Ahmed et al 2013 |
| **11** | ISP5 (glycerol-asparagine agar) | 0.8571 | +++ | Ahmed et al 2013 |
| **12** | ISP4 (inorganic salts-starch agar) | 0.4467 | ++ | Ahmed et al 2013 |
| **13** | ISP3 (oatmeal agar) | 0.8809 | +++ | Ahmed et al 2013 |
| **14** | ISP6 (peptone-yeast extract-iron agar) | 0.0044 | no growth | Ahmed et al 2013 |
| **15** | ISP1 (tryptone yeast extract agar) | 0.8836 | +++ | Ahmed et al 2013 |
| **16** | ISP7 (tyrosine agar) | 1.1966 | +++ | Ahmed et al 2013 |
| **17** | Medium without Carbon source | 0.000 | no growth | Contador et al 2015 |
| **18** | Medium without Nitrogen source | 0.000 | no growth | Contador et al 2015 |
| **19** | Medium without Sulfur source | 0.000 | no growth | Contador et al 2015 |
| **20** | Medium without Phosphate source | 0.000 | no growth | Contador et al 2015 |
| **21** | Glucose-Minimal Media Anaerobic | 0.000 | no growth | Ahmed et al 2013, Maldonado et al 2005 |
| **22** | Glucose-Minimal Media Aerobic | growth | growth | Ahmed et al 2013, Maldonado et al 2005 |
| **23** | D-Glucose as carbon source | 1.95 | growth | Contador et al 2015 |
| **24** | D-Mannose as carbon source | 1.95 | growth | Contador et al 2015 |
| **25** | D-Xylose as carbon source | 1.95 | growth | Contador et al 2015 |
| **26** | Glycerol as carbon source | 1.49 | growth | Contador et al 2015 |
| **27** | Lactose as carbon source | 0 | no growth | Contador et al 2015 |
| **28** | Sucrose as carbon source | 1.95 | growth | Contador et al 2015 |
| **29** | D-Fructose as carbon source | 1.95 | growth | Contador et al 2015 |
| **30** | Mannitol as carbon source | 1.95 | growth | Contador et al 2015 |
| **31** | Maltose as carbon source | 1.95 | growth | Contador et al 2015 |
| **32** | Acetate as carbon source | 0.99 | growth | Contador et al 2015 |
| **33** | D-Sorbitol as carbon source | 1.95 | growth | Contador et al 2015 |
| **34** | L-Arabinose as carbon source | 1.95 | growth | Contador et al 2015 |
| **35** | Citrate as carbon source | 1.95 | growth | Contador et al 2015 |
| **36** | L-glutamate as carbon source | 2.48 | growth | Contador et al 2015 |
| **37** | Glycine as carbon source | 0.99 | growth | Contador et al 2015 |
| **38** | Cellobiose as carbon source | 1.95 | growth | Contador et al 2015 |
| **39** | Raffinose as carbon source | 1.95 | growth | Contador et al 2015 |
| **40** | Uracil as carbon source | 0 | no growth | Contador et al 2015 |
| **41** | Uridine as carbon source | 2.07 | growth | Contador et al 2015 |
| **42** | D-Galactose as carbon source | 1.95 | growth | Contador et al 2015 |
| **43** | Lactate as carbon source | 0 | no growth | Contador et al 2015 |
| **44** | Adenosine as carbon source | 3.49 | growth | Contador et al 2015 |
| **45** | Trehalose as carbon source | 1.95 | growth | Contador et al 2015 |
| **46** | Glycine as nitrogen source | 1.95 | growth | Contador et al 2015 |
| **47** | Ammonium as nitrogen source | 1.95 | growth | Contador et al 2015 |
| **48** | Nitrate as nitrogen source | 1.95 | growth | Contador et al 2015 |
| **49** | Urea as nitrogen source | 3.01 | growth | Contador et al 2015 |
| **50** | L-glutamate as nitrogen source | 1.95 | growth | Contador et al 2015 |
| **51** | Nitrite as nitrogen source | 1.95 | growth | Contador et al 2015 |
| **52** | Inosine as nitrogen source | 3.93 | growth | Contador et al 2015 |
| **53** | L-glutamine as nitrogen source | 3.45 | growth | Contador et al 2015 |
| **54** | Adenosine as nitrogen source | 4.01 | growth | Contador et al 2015 |
| **55** | Sulfate as sulfur source | 1.95 | growth | Contador et al 2015 |
| **56** | Sulfite as sulfur source | 1.95 | growth | Contador et al 2015 |
| **57** | L-cysteine as sulfur source | 2.97 | growth | Contador et al 2015 |
| **58** | L-methionine as sulfur source | 2.34 | growth | Contador et al 2015 |
| **59** | Pyrophosphate as phosphorous source | 0 | no growth | Contador et al 2015 |
| **60** | Orthophosphate as phosphorous source | 1.9539 | growth | Contador et al 2015 |
| **61** | β-glycerolphosphate as phosphorous source | 0 | no growth | Contador et al 2015 |
| **62** | Salicin as carbon source | 0 | no growth | Maldonado et al 2005 |
| **63** | L-proline as carbon source | 2.48 | no growth | Maldonado et al 2005 |
| **64** | L-threonine as carbon source | 1.99 | no growth | Maldonado et al 2005 |
| **65** | L-tyrosine as carbon source | 2.01 | no growth | Maldonado et al 2005 |
| **66** | D-galactose as carbon source | 1.95 | growth | Maldonado et al 2005 |
| **67** | L-alanine as nitrogen source | 1.95 | no growth | Maldonado et al 2005 |

PCV = packed cell volumen; SS = synthetic seawater; CM: complex media

+++ = abundant growth in agar medium; ++ = moderate growth in agar medium

**Table S3:** Salinosporamide predicted production rates by iCC926 under different production conditions.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|   |  | **Sal A** | **Sal B** | **Sal A** | **Sal B** |  |
|   | **Medium** | **production** | **production** | **production** | **production** | **References** |
|   |  | ***in silico*****[mmol/gDW h]** | ***in silico*****[mmol/gDW h]** | ***in vivo*****[mg/L]** | ***in vivo*****[mg/L]** |  |
| **68** | Starch-SHY production media | 1.26  | 0.13 | 100  | 13  | Tsueng and Lam, 2009 |
| **69** | Starch-A1 production medium (SS) | 1.26  | 0.13 | 82.2-63.2  |   | Lechner et al, 2011 |
| **70** | Starch-production media plus butyric acid\* | 1.01  | 0.22 | 211  | 32.7  | Tsueng and Lam, 2007 |

\*experiment with *S. tropica* NPS21184; SS = synthetic seawater; Sal: salinosporamide.

**Table S4:** Salinosporamidepredicted production rates of mutant strains by iCC926.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|   |  | **Sal A** | **Sal A** | **Sal B** | **Sal B** |
|   | **Strain** | **production** | **production** | **production** | **production** |
|   |  | ***in silico*****[mmol/gDW h]** | ***in vivo******%*** | ***in silico*****[mmol/gDW h]** | ***in vivo******%*** |
| **71** | mutant salL- | 0 | n.d | 0.114 | yes |
| **72** | mutant salA- | 0 | n.d | 0 | n.d |
| **73** | mutant salT- | 0.63 | 50 | 0.117 | 91 |
| **74** | mutant salM- | 0.027 | 2.2 | 0.156 | 120 |
| **75** | mutant salH- | 0.048 | 3.8 | 0.091 | 70 |
| **76** | mutant salQ- | 0.315 | 25 | 0.127 | 98 |
| **77** | mutant salG- | 0 | n.d | 0.122 | 94 |
| **78** | mutant Strop\_3612- | 1.411 | 112 | 0.067 | 52 |
| **79** | mutant salL- with 5'-ClDA in the media | 2.3 | detected | 0.13 | detected |
| **80** | mutant salL- with 5-CIR in the media | 1.27 | detected | 0.11 | detected |
| **81** | mutant salL- with 5-CIRL in the media | 1.27 | detected | 0.11 | detected |
| **82** | mutant salL- with 5-CIRI in the media | 0.01 | detected | 0.126 | detected |
| **83** | mutant salG- with 5'-ClDA in the media | 0 | n.d | 0.119 | detected |
| **84** | mutant salG- with 5-CIR in the media | 0 | n.d | 0.119 | detected |
| **85** | mutant salG- with 5-CIRL in the media | 0 | n.d | 0.119 | detected |
| **86** | mutant salG- with 5-CIRI in the media | 0 | n.d | 0.119 | detected |

Reference: Eustáquio et al. 2009; Sal: salinosporamide; *in vivo* data: % with respect to wild-type; n.d: not detected

**Table S5:** Sporolidespredicted production rates by iCC926 assuming different production ratios.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|   | **Strain** | **Sporolide A** | **Sporolide B** | **Sporolide** | **Ratio** |
|   |   | ***in silico*****[mmol/gDW h]** | ***in silico*****[mmol/gDW h]** | ***in vivo*****[ug/L]** | **spo B:spo A** |
| **87** | Wild-type | 0.77 | 0.38 | 100 | 1:2 |
| **88** | Wild-type supplement with tyrosine | 0.906 | 0.453 | 100 |   |
| **89** | Wild-type | 0.578 | 0.578 | 100  | 1:1 |
| **90** | Wild-type supplement with tyrosine | 0.679 |  0.679 | 100 |   |
| **91** | Wild-type | 1.04 | 0.116 | 100 | 1:9 |
| **92** | Wild-type supplement with tyrosine | 1.22 | 0.136 | 100  |   |

Reference: McGlinchey et al 2008b; spo: sporolide

**Table S6:** Sioxanthinpredicted production rates by iCC926.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|   | **Strain** | **Sioxanthin** | **Sioxanthin** | **Reference** |
|   |   | ***in silico*****[mmol/gDW h]** | ***in vivo*** |  |
| **93** | Wild-type | 0.221 | detected | Richter et al 2015 |
| **94** | Strop2408mt | 0 | n.d | Richter et al 2015 |
| **95** | Strop3246mt | 0 | n.d | Richter et al 2015 |
| **96** | Strop3247mt | 0 |  n.d | Richter et al 2015 |
| **97** | Strop3248mt | 0 | n.d | Richter et al 2015 |

n.d: not detected

**Table S7:** Simulations of *Salinispora arenicola* iSACNH643 model under different growth conditions.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|   | **Medium** | **Growth rate** | **Growth rate** | **References** |
|   |  | ***in silico*** | **in vivo** |  |
|   |  | **1/h** |  |  |
| **1** | Medium without Carbon source | 0.000 | no growth | Contador et al 2015 |
| **2** | Medium without Nitrogen source | 0.000 | no growth | Contador et al 2015 |
| **3** | Medium without Sulfur source | 0.000 | no growth | Contador et al 2015 |
| **4** | Medium without Phosphate source | 0.000 | no growth | Contador et al 2015 |
| **5** | Glucose-Minimal Media Anaerobic | 0.000 | no growth | Ahmed et al 2013, Maldonado et al 2005 |
| **6** | Glucose-Minimal Media Aerobic | growth | growth | Ahmed et al 2013, Maldonado et al 2005 |
| **7** | Starch-A1 medium | 1.9698 | growth | This work |
| **8** | ISP2 (glucose-malt-yeast extract agar) | 1.0687 | +++ | Ahmed et al 2013 |
| **9** | ISP5 (glycerol-asparagine agar) | 0.9611 | +++ | Ahmed et al 2013 |
| **10** | ISP4 (inorganic salts-starch agar) | 0.5248 | ++ | Ahmed et al 2013 |
| **11** | ISP3 (oatmeal agar) | 0.6736 | +++ | Ahmed et al 2013 |
| **12** | ISP6 (peptone-yeast extract-iron agar) | 0.8502 | +++ | Ahmed et al 2013 |
| **13** | ISP1 (tryptone yeast extract agar) | 1.7004 | +++ | Ahmed et al 2013 |
| **14** | ISP7 (tyrosine agar) | 0.8822 | +++ | Ahmed et al 2013 |
| **15** | DMM | 0.1749 | growth | This work |
| **16** | Salicin as carbon source | 2.0839 | growth | Maldonado et al 2005 |
| **17** | L-proline as carbon source | 2.5271 | growth | Maldonado et al 2005 |
| **18** | L-threonine as carbon source | 2.3325 | growth | Maldonado et al 2005 |
| **19** | L-tyrosine as carbon source | 2.3958 | growth | Maldonado et al 2005 |
| **20** | D-galactose as carbon source | 0 | no growth | Maldonado et al 2005 |
| **21** | L-alanine as nitrogen source | 2.0839 | growth | Ahmed et al 2013 |
| **22** | L-glutamate as nitrogen source | 2.0839 | no growth | Ahmed et al 2013 |
| **23** | Sioxanthin production | 0.1941 mmol/gDW h | detected | Maldonado et al 2005; this work |

+++ = abundant growth in agar medium; ++ = moderate growth in agar medium

**Table S8:** Simulations of *Salinispora pacifica* iSPCNR114 model under different growth conditions.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|   | **Medium** | **Growth rate** | **Growth rate** | **References** |
|   |  | ***in silico*** | **in vivo** |  |
|   |  | **1/h** |  |  |
| **1** | Medium without Carbon source | 0.000 | no growth | Contador et al 2015 |
| **2** | Medium without Nitrogen source | 0.000 | no growth | Contador et al 2015 |
| **3** | Medium without Sulfur source | 0.000 | no growth | Contador et al 2015 |
| **4** | Medium without Phosphate source | 0.000 | no growth | Contador et al 2015 |
| **5** | Glucose-Minimal Media Anaerobic | 0.000 | no growth | Ahmed et al 2013, Maldonado et al 2005 |
| **6** | Glucose-Minimal Media Aerobic | growth | growth | Ahmed et al 2013, Maldonado et al 2005 |
| **7** | Starch-A1 medium | 1.3673 | growth | Ahmed et al 2013 |
| **8** | ISP2 (glucose-malt-yeast extract agar) | 0.9013 | +++ | Ahmed et al 2013 |
| **9** | ISP5 (glycerol-asparagine agar) | 0.8426 | +++ | Ahmed et al 2013 |
| **10** | ISP4 (inorganic salts-starch agar) | 0.9306 | ++ | Ahmed et al 2013 |
| **11** | ISP3 (oatmeal agar) | 0.5690 | +++ | Ahmed et al 2013 |
| **12** | ISP6 (peptone-yeast extract-iron agar) | 0.148 | +++ | Ahmed et al 2013 |
| **13** | ISP1 (tryptone yeast extract agar) | 1.48 | +++ | Ahmed et al 2013 |
| **14** | ISP7 (tyrosine agar) | 0.9853 | +++ | Ahmed et al 2013 |
| **15** | DMM | 0.1469 | growth | This work |
| **16** | L-alanine as nitrogen source | 1.8612 | no growth | Ahmed et al 2013 |
| **17** | L-glutamate as nitrogen source | 18612 | growth | Ahmed et al 2013 |
| **18** | Sioxanthin production | 0.1395 mmol/gDW h | detected | Ahmed et al 2013; this work |
| **19** | Lomaiviticin A production | 0.3633 mmol/gDW h | detected | Duncan et al 2015 |

+++ = abundant growth in agar medium; ++ = moderate growth in agar medium

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**Figure S5** Distribution of unique sets of reactions by subsystems. (a) ST-CNB440; (b) SA-CNH643; (c) SP-CNR114; (d) ST-CNB440/SA-CNH643; (e) ST-CNB440/SA-CNH643. Sets with 20 or more reactions were represented.

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