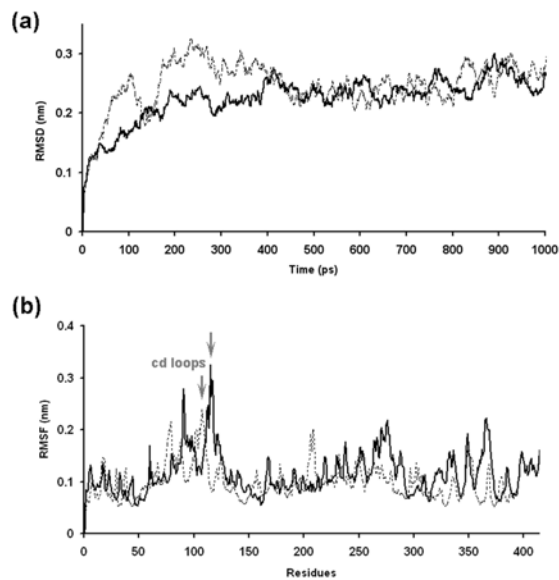


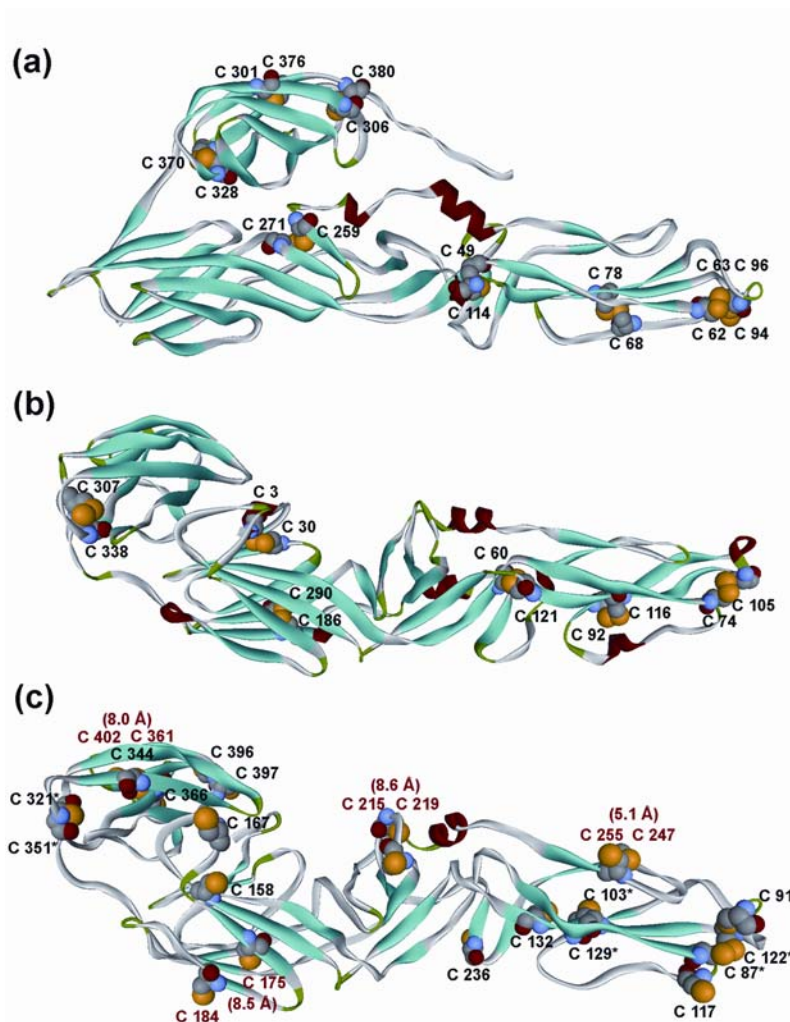
Supplementary Fig. S1. Sequence alignment of ANDV Gc and TBEV E proteins used as input for three-dimensional model building. Residues ranging from identical to weakly similar appear blue-coloured. In addition, identical residues are marked with black squares below the residue position bar. Secondary-structure predictions over the query sequence (P_SS) are indicated at the top of the alignment (E,e = β -strand; H,h = α -helix). Upper-case letters indicate a complete consensus for all nine secondary-structure predictor programs (see Methods). E_SS represents the secondary structure derived from the TBEV E crystallographic structure (PDBid: 1SVB). Coloured boxes indicate the location of residues according to domain topology of the 1SVB structure represented by Fig. 3. Green and pink lines indicate the location of the ANDV Gc FP candidate and the TBEV E FP, respectively.

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Supplementary Fig. S2. Molecular-dynamic trajectory analyses. (a) Root mean square backbone-atoms deviation (RMSD) ranging from their initial positions along a 1 ns simulation for the TBEV E crystal structure (1SVB) (dotted line) and the ANDV Gc model (solid line). The figure shows that the time-dependent change of backbone atoms from the initial structure remains between 2 and 3 Å, indicating that the local structure of each domain was mostly conserved during the simulation. The drift observed for the Gc model reaches a plateau after ~0.45 ns simulation. A similar behaviour was observed for the crystal structure. (b) Root mean square fluctuation (RMSF) (SD) of C α atoms of the TBEV E crystal structure (1SVB) (dotted line) and the ANDV Gc model (solid line). An averaging time period of 0.45–1 ns was chosen, based on the observation of the backbone RMSD drift. The cd-loop is marked with arrows in model and template simulations. Fluctuations over 2 Å are observed only in two loop regions, which agree with the high average temperature factors observed for the analogous region in resolved class II fusion proteins (Gibbons *et al.*, 2004).

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Supplementary Fig. S3. Comparison of the location of cysteine residues and disulfide bridges within crystallographic structures and the ANDV Gc model. Ribbon diagrams of (a) alphavirus E1 protein in the low-pH fusion conformation (PDBid: 1RER); (b) flavivirus E protein used as template for the Gc model development (PDBid: 1SVB); (c) molecular model for the ANDV Gc protein. Cys residues involved in disulfide bonds appear labelled in (a) and (b). In (c), Cys residues labelled with stars indicate disulfide bridges used in the model development. Cys residues in red indicate putative bonds (based on their $C\alpha$ distance) smaller than 10 Å.

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Supplementary Table S1. The best five hits of the threading program 3D-PSSM for ANDV Gc

Scoring values were taken in accordance to the relation between confidence and 3D-PSSM E-value (Karlin & Altschul, 1990).

Hit	Template length (aa)	Sequence identity (%)	3D-PSSM E-value	Protein	PDBid
1	369	23	0.03	Envelope glycoprotein E1of Sindbis virus	1LD4
2	169	19	1.67	Rob transcription factor, C-terminal domain	1D5Y
3	120	13	1.98	Bowman-birk trypsin inhibitor	1C2A
4	326	12	2.35	Human β 2-glycoprotein-I	1C1Z
5	121	14	2.73	Theor. model: human B-cell CD40 ligand-binding domain	1CDF

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Supplementary Table S2. The best five hits of the threading program LOOPP for ANDV Gc

The confidence-level estimations used are as follows: global alignment: Z-score 3.5 (95 % confidence), 3.0 (90 % confidence), 2.5 (60 % confidence); local alignment: Z-score 2.5 (95 % confidence), 2.0 (90 % confidence), 1.5 (60 % confidence).

Hit	Query sequence aligned (%)	Sequence identity (%)	Energy (all-atom)	Z-score		Protein	PDBid
				Global	Local		
1	98	27	-206.3	2.5	4.2	Human epidermal growth factor receptor	1MOX
2	78	27	-164.3	3.1	3.8	Envelope glycoprotein E of dengue 2 virus	1OK8
3	85	26	-118.5	0.6	0.9	Extracellular region of Rat Her2 (transferase)	1N8Y
4	85	23	-157.4	1.6	0.3	Type 1 insulin-like growth factor receptor (hormone receptor)	1IGR
5	84	24	-223.8	-0.9	-0.4	Human fascin, an actin cross-linking protein (structural protein)	1DFC

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Supplementary Table S3. The best five hits of the threading program FUGUE for ANDV Gc

The following scoring was applied: recommended cutoff: Z-score ≥ 6.0 (certain, 99 % confidence), other cutoff: Z-score ≥ 4.0 (likely, 95 % confidence), Z-score ≥ 3.5 (marginal, 90 % confidence), Z-score ≥ 2.0 (guess, 50 % confidence), Z-score < 2.0 (uncertain).

Hit	Template length (aa)	Z-score	Protein	PDBid
1	399	2.64	Horseradish peroxidase	1G5H
2	391	2.55	Envelope glycoprotein E1 of <i>Semliki Forest virus</i>	1RER
3	106	2.15	N-terminal domain of <i>N</i> -ethylmaleimide-sensitive factor	1QCS
4	28	2.09	Structure of Fsd-Ey peptide	1FME
5	73	1.98	Bovine heart cytochrome c oxidase	2OCC

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Karlin, S. & Altschul, S. F. (1990). Methods for assessing the statistical significance of molecular sequence features by using general scoring schemes. *Proc Natl Acad Sci U S A* **87**, 2264–2268.

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